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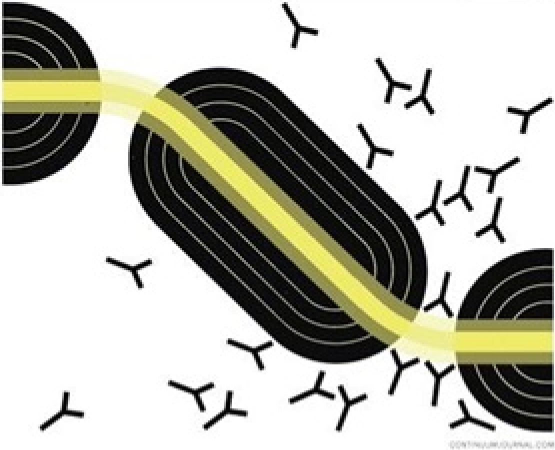
Peripheral Nerve and Motor Neuron Disorders

EDITOR-IN-CHIEF: LYELL K. JONES JR, MD, FAAN
GUEST EDITOR: KELLY GWATHMEY, MD



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Peripheral Nerve and Motor Neuron Disorders

Guest Editor: Kelly Gwathmey, MD

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CONTRIBUTORS[a]

Kelly Gwathmey, MD,
Guest Editor
Associate Professor of Neurology; Neuromuscular Medicine Division Chair, Virginia Commonwealth University, Richmond, Virginia

Relationship Disclosure: Dr Gwathmey has received personal compensation in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Alexion Pharmaceuticals, Inc, and in the range of $500 to $4999 for serving as a consultant for Alexion Pharmaceuticals, Inc, argenx, UCB S.A., and Xeris Biopharma and for serving on a speakers bureau for Alexion Pharmaceuticals, Inc.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Gwathmey reports no disclosure.

Said R. Beydoun MD, FAAN
Professor of Clinical Neurology; Richard Angus Grant Sr. Chair in Neurology; Division Chief, Neuromuscular Medicine; Program Director, Clinical Neurophysiology, Keck School of Medicine of USC, Los Angeles, California

Relationship Disclosure: Dr Beydoun has received personal compensation in the range of $500 to $4999 for serving as a consultant for Amylyx Pharmaceuticals, Biogen, Mitsubishi Chemical Group Corporation, Octapharma USA, Inc, and UCB S.A. and on a speakers bureau for Grifols S.A.; in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, Alnylam Pharmaceuticals, Inc, argenx, Janssen Global Services, LLC, and Takeda Pharmaceutical Company Ltd and on speakers bureaus for Amylyx Pharmaceuticals and CSL; and in the range of $10,000 to $49,999 for serving as a consultant for CSL and on speakers bureaus for Alexion Pharmaceuticals, Inc, Alnylam Pharmaceuticals, Inc, argenx, and Takeda Pharmaceutical Company Ltd. The institution of Dr Beydoun has received research support from Alexion Pharmaceuticals, Inc, Amylyx Pharmaceuticals, argenx, Genentech, Inc, Janssen Global Services, LLC, Regeneron Pharmaceuticals Inc, Sanofi, the Sean M. Healey & AMG Center for ALS, UCB S.A.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Beydoun discusses the unlabeled/investigational use of ibrutinib, IV immunoglobulin, and rituximab for the treatment of IgM–myelin-associated glycoprotein polyneuropathy.

[a] All relevant financial relationships have been mitigated.

Aimee Boegle, MD, PhD
Instructor, Harvard Medical School; Director, Neuromuscular Medicine Fellowship Associate Program Director, Neurology Residency, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Relationship Disclosure: Dr Boegle has received publishing royalties from Wolters Kluwer Health N.V.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Boegle discusses the unlabeled use of doxycycline, amoxicillin, and cefotaxime for the treatment of Lyme disease and the unlabeled use of gabapentin, lamotrigine, oxcarbazepine, pregabalin, selective norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine), topical anesthetics (eg, capsaicin, lidocaine), and tricyclic antidepressants (eg, amitriptyline, nortriptyline) for the treatment of neuropathic pain.

Brian Callaghan, MD, FAAN
Associate Professor of Neurology, Department of Neurology, University of Michigan, Ann Arbor, Michigan

Relationship Disclosure: Dr Callaghan has received personal compensation in the range of $500 to $4999 for serving as an editorial board member for the American Academy of Neurology, a consultant for Dynamed (EBSCO Industries, Inc), and a grant reviewer for the National Institutes of Health; in the range of $10,000 to $49,999 for serving as an expert witness for medicolegal work; and in the range of $50,000 to $99,999 for serving as an expert witness for the Vaccine Injury Compensation Program. The institution of Dr Callaghan has received research support from the American Academy of Neurology, JDRF (5COE-2019-861-S-B), the National Institute of Diabetes and Digestive Kidney Diseases (R01DK115687), and Veterans Affairs Clinical Science and Research Development.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Callaghan discusses the unlabeled use of amitriptyline, lamotrigine, oxcarbazepine, and venlafaxine for the treatment of painful distal symmetric polyneuropathy.

Leila Darki, MD
Assistant Professor of Clinical Neurology, Keck Medicine of USC, Los Angeles, California

Relationship Disclosure: Dr Darki has received personal compensation in the range of $0 to $499 for serving as a consultant for Guidepoint Global LLC and in the range of $500 to $4999 for serving as a consultant for Trinity Partners, LLC, and on scientific advisory or data safety monitoring boards for Amylyx Pharmaceuticals and Global Access Meetings.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Darki discusses the unlabeled/investigational use of ibrutinib, IV immunoglobulin, and rituximab for the treatment of IgM–myelin-associated glycoprotein polyneuropathy.

Melissa Elafros, MD, PhD
Assistant Professor, Department of Neurology, University of Michigan, Ann Arbor, Michigan

Relationship Disclosure: The institution of Dr Elafros has received research support from the National Center for Advancing Translational Sciences (UL1TR002240), the National Institute of Diabetes and Digestive and Kidney Diseases (P30-DK-02926 and P30-DK089503), and the National Institute of Neurologic Disorders and Stroke (5R25NS089450).

Unlabeled Use of Products/Investigational Use Disclosure: Dr Elafros discusses the unlabeled use of amitriptyline, lamotrigine, oxcarbazepine, and venlafaxine for the treatment of painful distal symmetric polyneuropathy.

Karissa Gable, MD
Associate Professor, Department of Neurology, Neuromuscular Division, Duke University Medical Center, Durham, North Carolina

Relationship Disclosure: Dr Gable has received personal compensation in the range of $500 to $4999 for serving as a consultant for Cowen Inc, MJH Life Sciences, WebMD, LLC, and on the scientific advisory or data safety monitoring boards for argenx, Immunovant, Inc, and Ultragenyx Pharmaceutical Inc and has received personal compensation in the range of $5000 to $9999 for serving on scientific advisory or data safety monitoring boards for Sanofi and Takeda Pharmaceutical Company Ltd and as a lecturer for WebMD, LLC.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Gable reports no disclosure.

Ali Habib, MD
Associate Professor; Director, Electrodiagnostic Laboratory, Department of Neurology, University of California, Irvine, California

Relationship Disclosure: Dr Habib has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for the National Institutes of Health/National Institute of Neurological Disorders and Stroke and UCB S.A., and as a consultant for Pfizer Inc and in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, argenx, Genentech, Inc, Immunovant, Inc, and UCB S.A., and for serving on speakers bureaus for Alexion Pharmaceuticals, Inc, and argenx. The institution of Dr Habib has received research support from Alexion Pharmaceuticals, Inc, argenx, Cabaletta Bio, Inc, Genentech, Inc, Immunovant, Inc, Regeneron Pharmaceuticals Inc, and UCB S.A.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Habib discusses the unlabeled/investigational use of IV immunoglobulin for the treatment of Guillain-Barré syndrome.

Leslie H. Hayes, MD
Instructor in Neurology, Harvard Medical School; Attending Physician, Boston Children's Hospital, Boston, Massachusetts

Relationship Disclosure: Dr Hayes has received personal compensation in the range of $500 to $4999 for serving as a consultant for PTC Therapeutics.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Hayes reports no disclosures.

[a] All relevant financial relationships have been mitigated.

Terry D. Heiman-Patterson, MD
Professor of Neurology; Director MDA/ALS Center of Hope, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania

Relationship Disclosure:
Dr Heiman-Patterson has received personal compensation in the range of $500 to $4999 for serving as a consultant for ITF Pharma, Mitsubishi Tanabe Pharma America, and Samus Therapeutics, Inc, and on scientific advisory or data safety monitoring boards for Amylyx Pharmaceuticals, Biogen, Biohaven Ltd, Cytokinetics, and Mitsubishi Tanabe Pharma America.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Heiman-Patterson reports no disclosure.

Aaron E. Izenberg, MD
Assistant Professor Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Relationship Disclosure: Dr Izenberg has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Biogen, F. Hoffman-La Roche Ltd, and Sanofi.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Izenberg reports no disclosure.

Peter Jin, MD
Assistant Professor, Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland

Relationship Disclosure: Dr Jin has received personal compensation in the range of $0 to $4999 for serving as a consultant for Ionis Pharmaceuticals.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Jin reports no disclosure.

Noah Kolb, MD
Associate Professor of Neurological Sciences, University of Vermont, Burlington, Vermont

Relationship Disclosure: Dr Kolb has received personal compensation in the range of $0 to $499 for serving as a consultant for Eisana Corp; in the range of $500 to $4999 for serving as a consultant for Abalone Bio, Inc, Alexion Pharmaceuticals, Inc, Lilly, and UCB S.A.; in the range of $5000 to $9999 for serving as a consultant for the National Institute of Neurological Disorders and Stroke and for serving as an expert witness for Locks Law and for Ralston, Pope & Diehl; and in the range of $10,000 to $49,999 for serving as an expert witness for Walkup, Melodia, Kelly & Schoenberger. The institution of Dr Kolb has received research support from the National Cancer Institute.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Kolb discusses the unlabeled use of baclofen-amitriptyline-ketamine, gabapentin, lidocaine, mexiletine, nortriptyline or amitriptyline, and pregabalin for the treatment of neuropathic pain.

CONTRIBUTORS[a] (CONTINUED)

Neeraj Kumar, MD
Professor of Neurology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota

Relationship Disclosure: Dr Kumar reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Kumar reports no disclosure.

Brendan McNeish, MD
Assistant Professor, Department of Physical Medicine Rehabilitation and Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania

Relationship Disclosure: Dr McNeish has received research support in the range of $100,000-$499,999 from the National Institutes of Health (NIA P30AG02482).

Unlabeled Use of Products/Investigational Use Disclosure: Dr McNeish discusses the unlabeled use of baclofen-amitriptyline-ketamine, gabapentin, lidocaine, mexiletine, nortriptyline or amitriptyline, and pregabalin for the treatment of neuropathic pain.

Pushpa Narayanaswami, MD, FAAN
Associate Professor of Neurology, Harvard Medical School; Vice Chair, Clinical Operations, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Relationship Disclosure: Dr Narayanaswami has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Alexion Pharmaceuticals, Inc, argenx, and Sanofi and for serving as a consultant for Novartis Pharmaceuticals Corporation; in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Janssen Global Services, LLC, and for serving as an editor, associate editor, or editorial advisory board member for *Muscle & Nerve*; and in the range of $10,000 to $49,999 for serving as a consultant for UCB S.A. Dr Narayanaswami has stock in Doximity, Inc, Dr Reddy's Laboratories Ltd, Moderna, Inc, Pfizer Inc, and Viatris Inc. Dr Narayanaswami has noncompensated relationships as a member of the boards of directors with the American Association of Neuromuscular & Electrodiagnostic Medicine and the Myasthenia Gravis Foundation Of America, Inc, that are relevant to the American Academy of Neurology interests or activities. The institution of Dr Narayanaswami has received research support from Alexion Pharmaceuticals, Inc.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Narayanaswami discusses the unlabeled use of doxycycline, amoxicillin, and cefotaxime for the treatment of Lyme disease and the unlabeled use of gabapentin, lamotrigine, oxcarbazepine, pregabalin, selective norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine), topical anesthetics (eg, capsaicin, lidocaine), and tricyclic antidepressants (eg, amitriptyline, nortriptyline) for the treatment of neuropathic pain.

[a] All relevant financial relationships have been mitigated.

Maryam Oskoui, MD, FAAN
Associate Professor, Department of Pediatrics, Department of Neurology and Neurosurgery, McGill University; Director, Division of Pediatric Neurology, McGill University Health Center, Montreal, Quebec, Canada

Relationship Disclosure: Dr Oskoui has a noncompensated relationship as a member of the medical and scientific advisory committee with Muscular Dystrophy Canada that is relevant to the American Academy of Neurology (AAN) interests or activities and has received personal compensation in the range of $500 to $4999 for serving as a member of the board of directors for the Association des Neurologues du Québec. The institution of Dr Oskoui has received research support from Biogen, the Canadian Institutes of Health Research, Genetech, Inc, Muscular Dystrophy Canada, and Santhera Pharmaceuticals.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Oskoui discusses the unlabeled/investigational use of celecoxib, E1v1.11, flunarizine, moxifloxacin, reldesemtiv rigosertib, salbutamol, and securinine for the treatment of spinal muscular atrophy.

Reza Sadjadi, MD
Assistant Professor in Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Relationship Disclosure: Dr Sadjadi has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Alnylam Pharmaceuticals, Inc, and the Dysimmune Diseases Foundation. The institution of Dr Sadjadi has received research support from the American Academy of Neurology.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Sadjadi reports no disclosures.

Laurent Servais, MD, PhD
Professor of Paediatric Neuromuscular Diseases, University of Oxford, Oxford, United Kingdom

Relationship Disclosure: Dr Servais has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Lupin Pharmaceuticals, Inc, and FibroGen, Inc, and as a consultant for Affinia Healthcare, Anagenesis Biotechnologies, Audentes Therapeutics, Catabasis Pharmaceuticals, Evox Therapeutics, Flamingo Therapeutics, RegenexBio Inc, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc; in the range of $5000 to $9999 for serving as a consultant for Biogen and Novartis AG; and in the range of $10,000 to $49,999 for serving as a consultant for F. Hoffman-La Roche Ltd and Pfizer Inc.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Servais discusses the unlabeled/investigational use of celecoxib, E1v1.11, flunarizine, moxifloxacin, reldesemtiv rigosertib, salbutamol, and securinine for the treatment of spinal muscular atrophy.

Jennifer Tracy, MD
Assistant Professor of Neurology, Division of Neuromuscular Medicine, Department of Neurology, Mayo Clinic, Rochester, Minnesota

Relationship Disclosure: Dr Tracy reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Tracy reports no disclosure.

Dr Tracy died September 26, 2023.

CONTRIBUTORS[a] (CONTINUED)

Waqar Waheed, MD
Professor of Neurology, Vice-Chair Department of Neurological Sciences, The University of Vermont and The University of Vermont Medical Center, Burlington, Vermont

Relationship Disclosure: Dr Waheed has received personal compensation in the range of $500 to $4999 for serving on a scientific advisory or data safety monitoring board for UCB S.A.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Waheed discusses the unlabeled/investigational use of IV immunoglobulin for the treatment of Guillain-Barré syndrome.

Self-Assessment and CME Test Writers

Douglas J. Gelb, MD, PhD, FAAN
Professor of Neurology, University of Michigan, Ann Arbor, Michigan

Relationship Disclosure: Dr Gelb has received personal compensation in the range of $500 to $4900 for serving as a multiple-choice question writer for *Continuum* with the American Academy of Neurology. Dr Gelb has received publishing royalties from a publication relating to health care.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Gelb reports no disclosure.

Nuri Jacoby, MD, FAAN
Associate Professor of Clinical Neurology, SUNY Downstate Health Sciences University; Attending Neurologist, Maimonides Medical Center, Brooklyn, New York

Relationship Disclosure: Dr Jacoby has received personal compensation in the range of $500 to $4999 for serving as a multiple-choice question writer for *Continuum* with the American Academy of Neurology and on scientific advisory or data safety monitoring boards for Alexion Pharmaceuticals, Inc and argenx and in the range of $5000 to $9999 for serving as an expert witness. The institution of Dr Jacoby has received research support from the American Board of Psychiatry and Neurology.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Jacoby reports no disclosure.

[a] All relevant financial relationships have been mitigated.

EDITOR'S PREFACE

The Former Frontier

Neurology has a long and rich history of announcing our arrival as a therapeutic specialty. We are so persistent in assuring prospective students that we no longer "diagnose and dismiss" or "diagnose and adios" that a reasonably skeptical listener might wonder why we insist so much. The reality of chronic neurologic disease and the massive complexity of the human nervous system have long established neurology as the final clinical frontier.

But what happens when you finally arrive at your horizon? There are now US Food and Drug Administration (FDA)–approved disease-modifying medications for the treatment of Alzheimer disease. We have numerous immunotherapies designed to target any of a number of autoimmune neurologic disorders at specific steps in the adaptive immunity cascade. A handful of non–cell-based gene therapies are on the market with many dozens in clinical trials, almost half of which are designed to treat previously intractable inherited neurologic conditions.

There are no better examples of the breathtaking therapeutic advances in neurology than the recent developments in peripheral nerve and motor neuron disorders. A gene therapy is now available for the treatment of spinal muscular atrophy, creating entirely new natural histories of this devastating neuromuscular disorder. An antisense oligonucleotide has been approved for the treatment of *SOD1*-associated amyotrophic lateral sclerosis (ALS). Novel, targeted immunotherapies are on the market for autoimmune neuromuscular disorders. Small molecule therapies are available for the treatment of patients with neuropathy caused by *TTR* amyloidosis. As this segment of our field leads the way forward in therapeutic development, an interesting transposition comes to mind: has neurology moved from the rearguard to vanguard of therapeutic innovation?

At an exciting time in neuromuscular medicine, Dr Kelly Gwathmey, our guest editor for this issue of *Continuum*, has gathered a series of topics and expert authors that will be indispensable to everyone from the novice to the expert clinician. The issue begins with an article by Dr Peter H. Jin outlining a rational approach to patients with suspected peripheral nerve disorders. Drs Ali A. Habib and Waqar Waheed provide a truly comprehensive update on the diagnosis and management of Guillain-Barré syndrome. Dr Karissa Gable reviews the chronic immune-mediated demyelinating neuropathies, including chronic inflammatory demyelinating polyradiculoneuropathy and its many variants and mimickers. The autoimmune axonal neuropathies receive an absolutely definitive discussion from Dr Jennifer A. Tracy. The protean manifestations of the diabetic neuropathies are covered by Drs Melissa A. Elafros and Brian C. Callaghan. Drs Aimee K. Boegle and Pushpa Narayanaswami outline everything the reader needs to know about infectious neuropathies. Neuropathic syndromes related to excess or deficiency are thoroughly reviewed by Drs Brendan L. McNeish, Noah Kolb, and Neeraj Kumar in their respective articles on toxic and nutritional neuropathies. The mysterious humors of the paraproteinemic neuropathies are clarified by Drs Said R. Beydoun and Leila Darki. Drs Leslie H. Hayes and Reza Sadjadi's article on hereditary neuropathies offers a thoughtful summary of a growing list of genetically mediated disorders. Advances in the diagnosis and treatment of ALS and other motor neuron diseases are thoughtfully reviewed by Dr Aaron Izenberg. Drs Maryam Oskoui and Laurent Servais deliver an

expert summary of the spectacular progress in the treatment of spinal muscular atrophy.

This issue of *Continuum* includes the second entry in our new article category, Selected Topics in Neurology Practice. These articles are designed to address important health care topics that complement our clinical reviews. High-quality, patient-centered management of chronic neurologic disorders requires teamwork across clinical disciplines. Models for integrated, coordinated delivery of services to our patients have been developed within the neuromuscular domain, and Drs Gwathmey and Terry D. Heiman-Patterson provide an excellent summary of these templates in their article, Multidisciplinary Clinics in Neuromuscular Medicine.

At an exciting time in neuromuscular medicine, Dr Kelly Gwathmey, our guest editor for this issue of Continuum, has gathered a series of topics and expert authors that will be indispensable to everyone from the novice to the expert clinician.

As always, after reading or listening to the content in this issue, subscribers can obtain up to 20 AMA PRA Category 1 Credits^{TM} toward self-assessment CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program [Section 3] of the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada with our posttest, written for the print issue by Drs Douglas Gelb and Nuri Jacoby.

There are certainly more neurologic cures in front of us than behind us. Moving through the immediate future of therapeutic development requires an ongoing sense of urgency, with no room for complacency. But as neurology arrives at the frontier and looks back to see others trying to catch up, we will have to address fresh challenges on behalf of our patients. New treatments are leading to unprecedented natural histories that need to be studied to reconstruct our definitions of success. Access, equity, and affordability will remain front of mind with expensive new therapeutics. Finally, if novel neurologic therapies are going to help patients, neurologists must feel capable and comfortable with their use. That is where *Continuum* comes in.

—LYELL K. JONES JR, MD, FAAN
EDITOR-IN-CHIEF

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Localization and Diagnostic Evaluation of Peripheral Nerve Disorders

By Peter H. Jin, MD

ABSTRACT

OBJECTIVE: This article provides a framework for the initial evaluation of patients with suspected peripheral nerve disease. The key clinical elements of peripheral nerve diseases can help the practicing neurologist differentiate among peripheral neuropathies with similar presentations.

LATEST DEVELOPMENTS: The wide range of peripheral nerve diseases with similar clinical presentations can pose a diagnostic challenge. The large array of available testing modalities (including imaging and electrodiagnostic, autonomic, laboratory, biopsy, and genetic testing) further complicates clinical decision making. Recent developments (eg, discovery of new autoantibodies, genetic variations, and histopathologic techniques) across the peripheral neuropathy spectrum have resulted in an increased need to evaluate patients logically and with a tailored diagnostic approach.

ESSENTIAL POINTS: A careful approach that focuses on key clinical elements combined with an understanding of purposeful diagnostic testing can lead to a successful diagnosis of peripheral nerve diseases.

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Address correspondence to Dr Peter H. Jin, 110 S Paca St, 3rd Floor, Baltimore, MD 21201, pjin@som.umaryland.edu.

RELATIONSHIP DISCLOSURE:
Dr Jin has received personal compensation in the range of $0 to $4999 for serving as a consultant for Ionis Pharmaceuticals.

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Dr Jin reports no disclosure.

INTRODUCTION

The practicing neurologist, regardless of specialty or practice environment, will encounter patients with potential peripheral nerve disorders. The presenting symptoms most associated with peripheral nerve disease (such as weakness, sensory disturbances, and imbalance) are nonspecific in isolation. Peripheral neuropathies with different etiologies can have identical clinical presentations, and even those with distinct localizations can have significant overlapping clinical findings. Furthermore, diseases outside of the peripheral nervous system can mimic peripheral nerve disease. Failure in differentiating between similar clinical presentations and identifying crucial diagnostic features can lead to misdiagnoses. A common disorder such as diabetic polyneuropathy may be misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) based on misinterpreted findings of an electrodiagnostic study.

Conversely, a devastating disorder such as amyotrophic lateral sclerosis presenting with right-hand weakness may be initially misdiagnosed as carpal tunnel syndrome, resulting in treatment-altering diagnostic delay. The wide spectrum of peripheral nerve diseases combined with their penchant for overlapping clinical phenotypes results in frequent diagnostic challenges.

Applying a clinical framework for patients with peripheral nerve disorders can help the practicing neurologist focus on specific differentiating clinical features that should ultimately yield a precise diagnosis. Several other reviews have detailed different approaches to peripheral nerve disorders and peripheral neuropathies.[1–3] This article focuses on the initial evaluation of these patients to prepare the reader to answer the following questions posed during an initial patient encounter:

- **Where should I direct my attention in the history and physical examination?**
- **What should I order for appropriate and efficient initial testing?**
- **Which red flags should I never miss?**

TERMINOLOGY

A foray into peripheral nerve disorders can be disorienting from the terminology perspective alone. Both the medical literature and clinical documentation from neuromuscular specialists use an array of localizations (eg, radiculoplexus neuropathy), acronym alphabet soup (eg, MADSAM [multifocal acquired demyelinating sensory and motor neuropathy], CANOMAD [chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies]), and pathologic terminology (eg, mixed sensorimotor with demyelinating and secondary axonal features). If the terminology and its rationale can be understood, then we can begin to appreciate the nuances of peripheral nerve disorders. Elements of peripheral nerve disorders are summarized in TABLE 1-1.

Using diabetic sensory polyneuropathy as an example, we can characterize the onset and rate of progression of this disorder as chronic and very slowly progressive. The anatomic distribution is symmetric and distal (ie, length-dependent, stocking-glove), with sensorimotor involvement that is heavily sensory predominant. The nerve fiber type involvement is a mixture of large and small fiber sensory and motor nerves. Electrodiagnostic and pathologic testing reveal primarily axonal degeneration. Dysautonomia is a commonly associated clinical feature. Diabetic sensory polyneuropathy is an acquired neuropathy that occurs in the context of the systemic medical disease diabetes. In summary, diabetic sensory polyneuropathy is an acquired, chronic, slowly progressive, length-dependent, sensory-predominant, mixed large and small fiber, primarily axonal polyneuropathy with common concomitant dysautonomia associated with a history of diabetes. With sufficient history, examination, and testing, every peripheral nerve disorder can be described within a similar framework with components of onset, pace of progression, modalities affected, anatomic distribution, electrodiagnostic features, affected nerve fiber type, and associated clinical context (TABLE 1-1). Furthermore, many peripheral nerve disease red flags are the opposite or inverse of the features of diabetic sensory polyneuropathy.

KEY POINTS

- **The clinical approach to peripheral nerve disorders should focus on identifying specific clinical elements in the history and examination that include onset, pace of progression, modalities affected, anatomic distribution, and affected nerve fiber types.**
- **Diabetic sensory polyneuropathy is an acquired, chronic, slowly progressive, length-dependent, sensory-predominant, mixed large and small fiber, primarily axonal polyneuropathy. This is a pattern commonly seen in polyneuropathies caused by toxic and metabolic etiologies.**
- **Red flag findings for peripheral nerve disorders include acute to subacute onset with rapid progression, motor-predominant involvement, early involvement of proprioception (early sensory ataxia), bulbar involvement, and a multifocal or non–length-dependent distribution.**

TABLE 1-1 **Clinical Elements of Peripheral Nerve Disease**

Clinical element	Differential diagnoses
Onset and pace of progression	
Chronic onset with gradual progression (months to years)	Toxic and metabolic polyneuropathies (eg, diabetes, chemotherapy related, vitamin B_{12} deficiency, alcohol related), human immunodeficiency virus (HIV) neuropathy, Charcot-Marie-Tooth disease (CMT) and hereditary neuropathies, multifocal motor neuropathy (MMN), motor neuron disease
Acute or subacute onset with rapid progression (days to months)	Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), paraproteinemic neuropathies, vasculitic neuropathies, Lyme disease neuropathy, hepatitis C–associated neuropathy, rheumatologic neuropathies
Anatomic distribution	
Length-dependent and symmetric	Toxic and metabolic polyneuropathies (eg, diabetes, chemotherapy related, vitamin B_{12} deficiency, alcohol related), human immunodeficiency virus (HIV) neuropathy, Charcot-Marie-Tooth disease (CMT), and hereditary neuropathies
Multifocal, non–length-dependent, or combination of distal and proximal involvement in motor, sensory, and muscle stretch reflex findings	GBS, CIDP, MMN, paraproteinemic neuropathies, vasculitic neuropathies, hepatitis C–associated neuropathy, Lyme disease neuropathy, rheumatologic neuropathies, motor neuron disease
Bulbar involvement with dysphagia, dysarthria, and dyspnea	GBS, motor neuron disease, myasthenia gravis, bulbar myopathy
Monomelic	Focal compression neuropathy, radiculopathy, plexopathy, early motor neuron disease
Sensorimotor involvement	
Prominent sensory involvement with minimal and late motor involvement	Toxic and metabolic polyneuropathies, HIV neuropathy
Prominent proprioception deficits	Sensory neuronopathies, dorsal column spinal cord disease
Pure motor involvement	MMN, motor neuron disease, myasthenia gravis, myopathy
Prominent early motor involvement alongside sensory involvement	GBS, CIDP, paraproteinemic neuropathies
Electrodiagnostic findings	
Distal or length-dependent axonal loss	Toxic and metabolic polyneuropathies, HIV neuropathy, paraproteinemic neuropathies
Multifocal or non–length-dependent axonal loss	Vasculitic neuropathies, hepatitis C–associated neuropathy, Lyme disease neuropathy, rheumatologic neuropathies, MMN, motor neuron disease
Segmental demyelination	GBS, CIDP, paraproteinemic neuropathies
Diffuse demyelination	CMT and hereditary neuropathies

HISTORY

Like other neurologic disorders, the diagnosis of peripheral nerve disorders begins with the history. Although the symptoms or reason for referral can be vague (eg, neuropathy, numbness), the clarification of discreet historical elements can set the foundation for guided examination and testing for efficient diagnosis.

Disease onset can range from hyperacute to chronic and is primarily inferred from the duration of a patient's symptoms. The most common peripheral nerve disorders are chronic and include neuropathies from toxic, metabolic, and genetic etiologies. Subacute onset is typically associated with progressive peripheral nerve diseases with an autoimmune or inflammatory etiology. Hyperacute- or acute-onset presentations are characteristic of autoimmune and occasionally infectious peripheral neuropathies, although localization to the central nervous system should also be considered in this setting.

The pace of progression should be considered separately from onset and refers to the temporal course of a patient's symptoms. Most peripheral nerve disorders follow a gradual, slowly progressive course. In toxic, metabolic, and genetic polyneuropathies, patients can have symptoms for years with barely noticeable or detectable decline. Differentiating between a monophasic versus a chronically progressive disorder is key to distinguishing the acute versus chronic autoimmune neuropathies (eg, Guillain-Barré syndrome [GBS] and diabetic lumbosacral radiculoplexus neuropathies are monophasic, whereas CIDP and nonsystemic vasculitic neuropathies are often chronically progressive with fluctuations). Rapid accumulation of peripheral nerve disorder deficits should spark consideration for autoimmune neuropathies and motor neuron disease. Similarly, a stepwise accumulation of deficits is highly suggestive of a vasculitic etiology. Alternatively, stepwise progression may be caused by the accumulation of a second, wholly different peripheral nerve disease (eg, cervical radiculopathy superimposed on carpal tunnel syndrome).

The anatomic distribution is broadly ascertained in the history. A symmetric and distal (ie, length-dependent, stocking-glove) distribution of sensorimotor symptoms is classically associated with genetic, toxic, and metabolic polyneuropathies. This pattern indicates a systemic etiology that affects the more metabolically vulnerable distal nerves. A monomelic distribution of sensorimotor symptoms can suggest a focal neuropathic process including compressive mononeuropathies, isolated radiculopathies, or rarely autoimmune conditions that impact the brachial and lumbosacral plexuses such as cervical or lumbosacral radiculoplexus neuropathy, multifocal motor neuropathy, or multifocal CIDP. A patchy distribution (ie, multifocal, non–length dependent) that is asymmetric and involves both proximal limb regions along with the face and trunk can suggest autoimmune neuropathies (eg, vasculitic neuropathies, sensory neuronopathies, acquired demyelinating neuropathies) where seemingly random segments of nerve root and peripheral nerve are "picked off" one by one. Anatomic distribution is further clarified via examination, electrodiagnostic testing, and imaging.

Consideration of nerve fiber involvement should include a comparison of both severity and time course regarding sensory and motor symptoms. Most peripheral nerve diseases are sensory predominant. Although most toxic, diabetic, and nutritional polyneuropathies can affect both sensory and motor function, sensory disturbances may precede motor involvement by years. Those patients with small fiber involvement often report "positive sensory symptoms"

such as neuropathic pain ("burning," "electrical"), allodynia, dysesthesia, and paresthesia. Those with large fiber sensory involvement, however, may report imbalance and incoordination. Importantly, positive sensory symptoms often represent an acquired cause of sensory polyneuropathy, whereas the absence of positive sensory symptoms is commonly encountered in genetic neuropathies. Motor involvement may not be noticed by the patient and might be detected by the examiner only through subtle findings of weakness or electrodiagnostic testing. In patients with sensory-predominant neuropathies, motor findings may still be present, but to a minimal degree, and manifest as mild toe flexor and toe extensor weakness. Findings of motor involvement that precede or are out of proportion to sensory findings should alert the examiner to the possibility of motor neuron disease or multifocal motor neuropathy, although motor involvement can be appreciated in more chronically progressive genetic neuropathies (eg, Charcot-Marie-Tooth disease).

Concomitant autonomic dysfunction (ie, dysautonomia) is associated with many systemic peripheral nerve disorders. Symptoms associated with dysautonomia include sensitivity to light, orthostatic presyncope or syncope, early satiety from poor gastric emptying, sicca symptoms, constipation, diarrhea, erectile dysfunction, vaginal dryness, and anhidrosis. The recognition of dysautonomia can affect both diagnosis and patient symptom management. Dysautonomia is particularly common in diabetic polyneuropathy and GBS and is a hallmark of amyloid polyneuropathy (the hereditary transthyretin form of which is treatable with RNA silencer therapy).

Various systemic medical diseases are associated with neuropathies. A careful medical history and review of systems can reveal risk factors for neuropathies that include diabetes, cancer, chemotherapy exposure, alcohol use disorder, rheumatologic disorders, and vitamin deficiencies.

Peripheral nerve diseases can also be broadly categorized as hereditary, acquired, or idiopathic. Inquiring about developmental and childhood history can reveal subtle clues to long-standing neuromuscular dysfunction. A careful family history may reveal specific diagnoses as well as a potential undiagnosed history of peripheral nerve disease. Asking patients about family members with a history of ambulation and pain disorders can reveal a latent family history of peripheral nerve disease.

PHYSICAL EXAMINATION

The neurologic examination of peripheral nerve disorders naturally relies heavily on motor, sensory, and muscle stretch reflex components. Other elements of the neurologic examination should not be de-emphasized, however, because alternative neurologic localizations may account for some "neuropathic" patterns. Careful cranial nerve examination is particularly important. Cranial neuropathies are seen in some peripheral nerve disorders, primarily those with a multifocal or non–length-dependent anatomic distribution. Facial strength and eye movement are frequently affected in GBS. Tongue and oropharyngeal weakness are common in motor neuron disease. Tonic pupils may be suggestive of dysautonomia.

The motor and reflex examination contains the key elements for determining the anatomic distribution of a possible peripheral disorder. A patient's distribution of muscle weakness, atrophy, and diminished muscle stretch reflexes may triangulate to a specific lesional localization (focal and asymmetric

peripheral nerve disease, eg, entrapment neuropathy) or a specific anatomic distribution (eg, symmetric, distal, multifocal). Although most peripheral nerve disorders are associated with diminished or absent muscle stretch reflexes, they remain normal in small fiber polyneuropathies and very distal large fiber polyneuropathies and are expected to be hyperactive in amyotrophic lateral sclerosis. The motor and reflex examination may also reveal a central nervous system mimic. Careful examination for upper motor neuron signs should include assessment of relative hyperreflexia (presence of a normal muscle stretch reflex in the presence of an associated weak muscle) and pathologic reflexes (toe responses, Hoffman response, frontal release signs, brisk jaw jerk reflex).

The sensory examination, although rife with poor interrater reliability because of examiner and patient subjectivity, is critical for several reasons. First, a careful sensory examination revealing normal findings suggests a possible motor-predominant or pure motor pattern. Second, it provides information regarding nerve fiber type involvement. The presence of deficits in vibration or proprioception sense may suggest a localization to large fibers or their related proximal pathways (eg, dorsal columns). The rare but striking presentation of profound proprioceptive deficits, sometimes involving joint position loss of the knees and hips, may be suggestive of an acquired demyelinating polyneuropathy or a sensory neuronopathy. A sensory examination with isolated deficits in pin and temperature sense with otherwise normal vibration and joint position sense may favor the diagnosis of a small fiber neuropathy. Lastly, a careful sensory examination may reveal sensory signs even when a patient does not report sensory symptoms.[4]

Because of the subjective nature of the sensory examination, quantitative and validated methods of testing are helpful. For vibration testing, the use of a quantitative 64-Hz Rydel-Seiffer tuning fork can more precisely quantify the degree of vibration sense deficit. Unlike a traditional qualitative 256-Hz tuning fork, the quantitative 64-Hz tuning fork findings correlate with abnormal sensory nerve action potential findings on nerve conduction studies.[5,6] Testing general sensation of the distal foot with a monofilament fiber has been repeatedly validated in the detection of diabetic sensory polyneuropathy and can be helpful as a screening tool. A 10-g monofilament test of the toes and feet has been validated to be highly predictive of diabetic foot ulcers and has similar sensitivity and specificity for ulcer risk assessment as a qualitative 256-Hz tuning fork assessment.[7,8] A less stiff 1-g or 2-g monofilament has been shown to be more sensitive for the detection of diabetic sensory polyneuropathy than the standard 10-g monofilament.[9] Biothesiometry devices deliver adjustable voltages of vibration stimulus that are highly precise and validated. It may be marginally better than tuning fork and monofilament testing for neuropathy detection, but the cost of the device is likely a barrier for most practicing neurologists. Similarly, various quantifiable thermal stimulus devices have been validated to detect small fiber dysfunction, but their lack of incremental benefit over pin sensation and monofilament testing makes their use difficult to justify.[10]

Of note, an age-related decline occurs in vibration sense and ankle jerks in patients aged older than 65 years.[11] Peripheral nerve disease is unlikely in older adult patients with isolated findings of absent ankle reflexes and mild decreased vibration sense in the feet without other associated historical or examination elements.

KEY POINTS

- **Positive sensory symptoms often represent an acquired cause of sensory polyneuropathy, whereas the absence of positive sensory symptoms is commonly encountered in genetic neuropathies.**

- **Subtle findings of motor weakness in patients with chronic, sensory-predominant, axonal polyneuropathies may include mild toe flexor and toe extensor weakness.**

- **Prominent symptoms of chronic dysautonomia in a patient with an idiopathic neuropathy should prompt evaluation for amyloid neuropathy.**

- **Vibration sense testing with a quantitative tool such as a Rydel-Seiffer tuning fork allows for more objective measurements that can be tracked over time and correlate more directly to electrodiagnostic testing.**

- **Peripheral nerve disease is unlikely in older adult patients with isolated findings of absent ankle reflexes and mild decreased vibration sense in the feet without other associated historical or examination elements.**

CASE 1-1

A 67-year-old right-handed man with a history of type 2 diabetes, hypertension, and lung cancer presented to the neurology office reporting hand weakness. About 1 year before presentation, the patient noticed hand grip weakness in the left hand. About 4 months later, he started to have similar symptoms in his right hand. He had noted muscle wasting in his hands and forearms. He denied sensory symptoms in his upper extremities. He had more remote symptoms of numbness and tingling in his feet, which he reported began soon after he received chemotherapy with cisplatin about 5 years earlier and overall had been stable without progression.

On examination, he had normal mental status and cranial nerve function. Examination of the upper extremities revealed weakness in bilateral finger abduction, which was worse on the left. He had moderate atrophy in the hypothenar eminence and first dorsal interossei bilaterally. Fasciculations were frequent in the bilateral first dorsal interossei. Strength examination of the lower extremities was normal. His muscle stretch reflexes were absent throughout. He had absent Babinski and Hoffman signs. Sensory examination of the feet revealed severe loss of vibration sensation and pinprick sensation up to the midshin. In the upper extremities, vibration testing of the second digit was normal, and pinprick testing revealed mild loss of sharp sensation in the right thumb and second digit. The patient was evaluated via electrodiagnostic testing and laboratory testing, which led to a diagnosis of multifocal motor neuropathy with associated GM1 antibodies superimposed on a more long-standing length-dependent sensorimotor peripheral neuropathy and median neuropathy at the wrist.

COMMENT

This case illustrates the layering of clinical elements commonly encountered in peripheral nerve disease. Rather than classifying the onset and pace of progression of all symptoms together, the neurologist must parse the potential clinical entities and describe them accordingly. Although the patient had sensory neuropathy symptoms for many years in the feet, possibly from diabetes or chemotherapy (sensorimotor peripheral neuropathy), the most striking part of his presentation is the progressive hand weakness findings in the past year that may suggest a superimposed disorder (multifocal motor neuropathy). Although there is a combination of sensorimotor findings, the clinical details regarding the hand symptoms reveal a strong motor predominance with notable atrophy and muscle strength loss with only minimal associated sensory deficits. The pinprick loss in the right first and second digits represents an incidentally discovered carpal tunnel syndrome (median neuropathy at the wrist) that overlaps with his subacute motor-predominant hand symptoms.

In addition to the neurologic examination, a general medical examination can reveal evidence of undiagnosed systemic medical diseases or hereditary diseases. Orthostatic blood pressure testing can help screen for autonomic insufficiency. The clinician should give particular attention to the skin and joints, which may provide the basis for suspicion of rheumatologic disorders and hereditary peripheral nerve disorders. Asking the patient to change into a gown can aid in the inspection of skin and joints. Inspection of skin and joints can reveal facial erythema, joint enlargement and deformities of the fingers, areas of hyperpigmentation and hypopigmentation, and livedo reticularis and racemosa, which may suggest rheumatologic disease. In the feet, the presence of high arches (ie, pes cavus) and hammer toes may suggest hereditary neuropathy (ie, Charcot-Marie-Tooth disease) or other long-standing neuropathies. In patients with neuroma-forming diseases such as neurofibromatosis or leprosy, palpation of extremities may reveal subcutaneous mass lesions.

DIFFERENTIAL DIAGNOSIS

After a comprehensive history and physical, the initial evaluation of a potential peripheral nerve disorder will usually generate a substantial list of differential diagnoses. Many presentations of peripheral nerve disorders are nonspecific and require further elucidation via additional laboratory and electrodiagnostic workup. This is particularly true for the etiology, as peripheral nerve disorders of various etiologies can have identical clinical presentations. For example, a chronic, slowly progressive, length-dependent sensory polyneuropathy from diabetes, HIV, and kidney disease can present similarly on examination. Also, Hickam's dictum, or the absence of a singular parsimonious diagnosis, applies routinely in neuromuscular settings. Separate disease processes with distinct localizations can mimic or magnify symptoms of the peripheral nerve disease of interest and lead to a layering effect, where multiple neurologic localizations can contribute to the same clinical findings (CASE 1-1). For example, a patient presenting with a foot drop may have a simultaneous contribution from a focal fibular mononeuropathy and an L5 radiculopathy.

When considering a neuromuscular diagnosis, the most likely alternatives typically localize to other parts of the peripheral nervous system. Cervical and lumbar radiculopathies can mimic focal mononeuropathies and, if bilateral, can also mimic polyneuropathies. Myopathies and neuromuscular junction disorders can mimic pure motor neuropathies. In the central nervous system, myelopathies can present with bilateral symmetric sensorimotor abnormalities, and a parafalcine brain lesion can present with bilateral lower extremity sensorimotor deficits. Many symptoms and signs of central nervous system disorders (eg, weakness, numbness, ataxia, dysautonomia) overlap with peripheral nerve disorders. The evaluation of central nervous system disorders may be further complicated by the concomitant presence of peripheral nervous system disease, which can mask the expected upper motor neuron findings.

Non-neurologic disorders can also mimic peripheral nerve diseases. Musculoskeletal disorders including joint disorders and tendinopathies can mimic the pain and fatigue of neuropathies. Chronic pain conditions such as fibromyalgia and complex regional pain syndrome can present similarly to polyneuropathies with numbness, tingling, and burning pain.

KEY POINTS

- **Skin and joint examination can reveal key diagnostic elements in diseases of peripheral nerves. Ideally, patients should change into a gown to allow for inspection of the proximal extremeties and trunk.**
- **Patients with potential peripheral nerve disorders may have multiple diagnoses that overlap. Although this overlap is most common with other peripheral nerve disorders, disorders of the central nervous system can also manifest with symptoms and signs traditionally associated with the peripheral nervous system.**
- **Non-neurologic disorders can mimic peripheral nerve disease and should be considered in the presence of inconsistent neurologic examination findings and electrodiagnostic testing.**

DIAGNOSTIC EVALUATION

Beyond the history and examination, diagnostic testing for peripheral nerve disorders includes electrodiagnostic studies, autonomic function tests, laboratory studies, imaging, and biopsy. The choice of tests and order to pursue them is based on the initial clinical impression.

Electrodiagnostic Testing

Electrodiagnostic testing is the most common diagnostic tool for patients with suspected peripheral nerve disorders. The standard components include nerve conduction studies and needle EMG, collectively referred to as *electrodiagnostic testing*, which is considered an extension of the neurologic examination. Electrodiagnostic testing can help clarify historical and examination elements by demonstrating a neuropathy's anatomic distribution and nerve fiber type involvement. Nerve conduction studies can elegantly demonstrate a predominance of sensory or motor nerve conduction deficits. Nerve conduction studies and EMG both can assist in determining if a peripheral nerve disease is length dependent (distal), proximal, or multifocal and provide more precise localization for peripheral nerve disorders. For example, a patient with interossei weakness assessed to have potential ulnar neuropathy at the elbow may be determined by electrodiagnostic studies to instead have an ulnar neuropathy at the wrist. A patient with distal vibration loss in the feet with absent lower extremity reflexes who is clinically assessed to have a length-dependent sensory polyneuropathy may be revealed by electrodiagnostic evaluation to instead have bilateral S1 radiculopathies. Furthermore, electrodiagnostic studies can reveal nerve fiber involvement not apparent on history and examination alone. For example, in a patient with primarily sensory clinical findings, electrodiagnostic testing may demonstrate a mixed sensorimotor nerve disorder.

EMG specifically can elucidate the chronicity of peripheral nerve disorders if a motor component exists. The earliest EMG abnormality in acute motor processes is reduced recruitment of motor unit action potentials. Over time, with chronic reinnervation, motor unit potentials will have a higher amplitude and longer duration. This process takes months to occur and would not be expected in the acute setting. If there is active or ongoing denervation (axonal loss) for at least 14 to 21 days, EMG may show fibrillation potentials. Although fibrillation potentials may resolve with reinnervation in a monophasic disorder, their presence may persist in diseases where denervation progresses, such as in motor neuron disease. Sometimes EMG findings can be dissonant with clinical findings as well. For example, a patient with neuropathy symptoms for only a few months may have EMG findings that suggest a more chronic process, which can help inform diagnosis.

Unlike the history and examination, electrodiagnostic evaluation can differentiate the presence of an axonal versus demyelinating peripheral nerve disorder. Although certain historical and examination features may be more suggestive of a demyelinating disorder (eg, diffuse areflexia, proximal and distal weakness), it can be confirmed via electrodiagnostic studies. Furthermore, electrodiagnostic evaluation can help distinguish patterns of demyelinating peripheral nerve disorders as acquired versus hereditary. For example, acquired demyelinating disorders are commonly associated with compound muscle action potential temporal dispersion or conduction block.

Similar to a neurologic examination, electrodiagnostic evaluation is better equipped to clarify localization than specify disease etiology. Electrodiagnostic results must be interpreted in the clinical context and other supportive testing. As a corollary for the practicing neurologist, an electrodiagnostic evaluation request should include both relevant clinical details and diagnostic considerations. Each electrodiagnostic evaluation is uniquely tailored for the specific patient based on the clinical context. The absence of this clinical context can result in uninformative electrodiagnostic studies.

Not all patients with peripheral neuropathy require an electrodiagnostic evaluation. A common rationale for deferring electrodiagnostic testing is that the results do not alter the clinical impression and will not change management. Even in patients with distal sensory neuropathies, electrodiagnostic testing has been shown to not only change management but also change diagnosis and provide additional diagnoses.[12] However, patients with known diabetic sensory polyneuropathy with no red flag symptoms typically do not need to undergo electrodiagnostic evaluation. Electrodiagnostic studies can be helpful to parse overlapping peripheral nervous system diseases and can help to discover unexpected diagnoses such as rare “mimicker” peripheral nerve disorders.

KEY POINT

- **Except in clinically definitive cases, electrodiagnostic testing should be considered for most patients with peripheral nerve disease because there are many mimics with similar clinical presentations. Electrodiagnostic testing often identifies the presence of multiple concomitant diseases.**

Autonomic Function Testing

Autonomic function testing should be considered in the workup of peripheral nerve disorders. Dysautonomia is a prominent component of many neuropathy syndromes. In particular, it is commonly seen in diabetic neuropathies, amyloid neuropathies, and GBS. Because of the nonspecific nature of dysautonomia symptoms and many non-neurologic mimics (eg, lightheadedness, heart palpitations, gastrointestinal symptoms, temperature intolerance), obtaining autonomic function testing can be useful to ascertain if a related deficit in the autonomic nervous system is present.

Autonomic function testing is not universally available, and testing protocols are variable. Autonomic function testing generally includes tests of cardiovascular adrenergic function, cardiovagal function, and sudomotor function. Testing of cardiovascular adrenergic function involves a tilt-table test and Valsalva test. Testing of cardiovagal function includes heart rate variability to breathing and determination of the Valsalva ratio. Sudomotor function testing is carried out in two ways. Quantitative sudomotor axon reflex testing (QSART) evaluates postganglionic sympathetic sudomotor function via measuring sweat response to acetylcholine that is iontophoresed into the skin. QSART can be helpful in diagnosing and characterizing small fiber neuropathy and distinguishing peripheral from central causes of dysautonomia (in which the QSART is normal). Thermoregulatory sweat testing can evaluate both preganglionic and postganglionic sudomotor function. In this test, a powder indicator that changes color with sweat is applied to the patient’s body surface. The patient is then placed in a controlled environment with monitoring of ambient temperature, skin temperature, and humidity. Digital photographs and computerized images are captured to assess for distributions of anhidrosis.[13]

Serum Laboratory Testing

Serum laboratory testing can help determine the specific etiology of peripheral nerve disorders, and some patients may have multiple etiologies. The American Academy of Neurology recommends testing for fasting glucose, vitamin B_{12}

TABLE 1-2 **Recommended Blood Testing for Patients With Peripheral Nerve Disorders[a]**

Consider in all patients

- Basic metabolic function panel with fasting glucose
- Complete blood cell count
- Liver function
- Vitamin B_{12}
- Methylmalonic acid with or without homocysteine
- Serum protein electrophoresis with immunofixation
- Antinuclear antigen
- Sjögren syndrome antibodies A and B (anti-Ro, anti-La)

Consider in select patients depending on risk factors and clinical findings

- 2-Hour glucose tolerance test
- Hemoglobin A_{1c}
- Thyroid function
- Vitamin B_1 whole blood
- Vitamin E
- Vitamin B_6
- Copper
- Zinc
- Human immunodeficiency virus (HIV)
- Lyme disease
- Hepatitis B and hepatitis C
- Cryoglobulin
- Rheumatoid factor
- Erythrocyte sedimentation rate
- C-reactive protein
- Antigliadin antibodies
- Antitransglutaminase antibodies
- Antineutrophil cytoplasmic antibodies
- Serum light chains
- Urine electrophoresis, immunofixation, and light chains
- Ganglioside antibodies
- Paraneoplastic antibodies
- Genetic testing for neuropathy

[a] Modified with permission from Jin PH, Clin Geriatr Med.[26] © 2021 Elsevier Inc.

deficiency, and monoclonal gammopathies as the highest-yield blood tests for peripheral neuropathy.[14] Previous practice guidelines recommended testing for monoclonal gammopathies only in patients older than 50 years, but this age cutoff has since been removed because of the increased prevalence of monoclonal gammopathy of undetermined significance and multiple myeloma in younger patients.

When testing for monoclonal gammopathy disorders, ordering both a serum protein electrophoresis and immunofixation increases diagnostic sensitivity.[15] Beyond these tests, limited evidence-based guidance exists. In patients with atypical, acute, or subacute, non–length-dependent presentations, expanded laboratory testing will be necessary. Peripheral nerve disease can be a heralding presentation in various other diseases, particularly rheumatologic disorders, which may warrant further testing in some patients.[16-18]

Complicating the challenge of testing for etiology, specifically in distal polyneuropathies, is the entity of idiopathic polyneuropathies. Despite thorough workup, 11% to 31% of polyneuropathy cases have no identifiable cause.[19] Repeat laboratory testing generally does not yield additional information.[20,21] Some of these cases have been classified as chronic idiopathic axonal polyneuropathy, which typically occurs between the ages of 50 to 60 years, and has a generally benign course.[19,22] Previously classified idiopathic neuropathies are occasionally revealed to be adult-onset hereditary neuropathies. Genetic testing should be considered in patients with phenotypes expected in genetic neuropathies and in those with a family history of these conditions. An example of a genetic phenotype is neuropathy secondary to transthyretin amyloidosis, which presents as idiopathic sensorimotor polyneuropathy, bilateral carpal tunnel syndrome, lumbar stenosis, and dysautonomia. Currently, evidence is insufficient to suggest routine genetic testing in patients with idiopathic neuropathy.[14,23] This practice decision is complicated by the evolving context of increased accessibility to genetic testing, the advances in specific disease-modifying treatment for hereditary neuropathies (namely hereditary transthyretin amyloidosis polyneuropathy), and the greater understanding of the clinical heterogeneity and nonspecific presentations of hereditary peripheral nerve disorders.[24,25] For a summary of recommended blood tests for polyneuropathy, see **TABLE 1-2**.[26]

CSF testing is occasionally warranted in the evaluation of peripheral nerve disorders. Albuminocytologic dissociation can be helpful as a secondary diagnostic marker for immune-mediated polyradiculoneuropathies such as CIDP. Tests of malignancy including cytology and flow cytometry can be diagnostic of neurolymphomatosis and carcinomatous meningitis. Testing for cerebrospinal pleocytosis and microbial markers can establish a diagnosis for an infectious polyneuropathy.

Peripheral Nerve Imaging

Peripheral nerve imaging can add diagnostic value in the correct context. Precise diagnosis via clinical findings and electrodiagnostic testing can be limited by various factors. Layering of multiple peripheral nerve diseases can lead to electrodiagnostic test results that are difficult to interpret definitively. For example, a patient with a sensorimotor distal polyneuropathy may have their physical examination findings and electrodiagnostic testing results clouded by an incidental presence of a lumbar radiculopathy. Additionally, the differentiation

KEY POINTS

- **All patients with sensory peripheral neuropathy should be tested for fasting blood glucose, vitamin B_{12} levels, and serum electrophoresis with immunofixation.**

- **Patients with idiopathic sensorimotor polyneuropathy, bilateral carpal tunnel syndrome, lumbar stenosis, and dysautonomia should be considered for amyloid testing including genetic testing for hereditary transthyretin amyloidosis.**

of peripheral nerve disease based on clinical and electrodiagnostic findings becomes increasingly more difficult in more advanced and severe presentations. For example, advanced forms of a demyelinating peripheral nerve disease such as CIDP can demonstrate findings of secondary axonal loss on electrodiagnostic testing. Also, in the context of very proximal conduction block, routine nerve conduction studies may fail to capture findings of acquired demyelination sufficient to make a diagnosis, and imaging may enable diagnosis.[27]

MRI is a common diagnostic tool in the evaluation of peripheral nerve disorders. Most commonly, MRI of the spine is considered to evaluate for differential diagnoses of radiculopathy and myelopathy. MRI of the extremities, particularly MRI neurography, can assess for extraneural and intraneural mass lesions, abnormal signal and enlargement of nerves, contrast-enhancement of nerves suggestive of blood-nerve barrier breakdown, and nerve continuity.[28]

Neuromuscular ultrasound is a validated tool for the evaluation of peripheral nerve disorders.[29] The most common application in peripheral nerve disease is the measurement of a cross-sectional area of peripheral nerves in the limb. Neuromuscular ultrasound can determine areas of focal enlargement indicative of focal or multifocal neuropathic disease. Although the most validated use of neuromuscular ultrasound is the identification of common focal compressive mononeuropathies such as carpal tunnel syndrome, the same principle of identifying focal enlargement has been applied to the diagnosis of autoimmune multifocal demyelinating polyneuropathies such as CIDP and multifocal motor neuropathy.[30] A pattern of focal areas of enlargement is distinct from axonal peripheral nerve diseases such as distal sensory polyneuropathy, where the peripheral nerve caliber is unchanged or mildly diffusely increased. Additionally, neuromuscular ultrasound can identify fasciculations, mass lesions, myopathy, muscle denervation, nerve continuity in traumatic injury, and the presence of intraneural vascularity via power Doppler.[31]

Both MRI and neuromuscular ultrasound of peripheral nerves carry their strengths and weaknesses. Neuromuscular ultrasound provides higher resolution of peripheral nerve anatomy compared with MRI, but neuromuscular ultrasound is limited by sonographic penetrance and has limited utility for studying deep nerves such as the sciatic nerve in the thigh.[32] Neuromuscular ultrasound carries the advantage of dynamic imaging and can assess for fasciculations, compressibility, muscle and tendon subluxation, and vascular flow. Neuromuscular ultrasound technical proficiency is less common and is less accessible compared with MRI. Unlike MRI, neuromuscular ultrasound is not yet validated for contrast-enhanced studies.[33]

Skin Biopsy

Skin biopsy can assist in the evaluation of small fiber neuropathy. Testing is typically pursued in select clinical contexts if evaluation for a polyneuropathy via electrodiagnostic studies is normal. Testing involves a 3-mm punch biopsy of a single limb (generally lower extremity) at sites of interest including the distal leg, distal thigh, and proximal thigh. Biopsy samples are assessed for intraepidermal nerve fiber density, which is expected to be reduced in small fiber neuropathies. The pattern of density loss can also speak to the distal (length-dependent) or multifocal (non–length-dependent) nature of the neuropathy. In addition to intraepidermal nerve fiber density, biopsy samples can be stained to assess for

the presence of amyloid deposition and for sudomotor innervation of sweat glands.[34]

Nerve Biopsy

Nerve biopsy is considered in cases of progressive peripheral nerve disease without identified etiology. A sensory nerve is typically selected, most commonly the sural nerve. Nerve biopsy remains most useful in cases of suspected vasculitic neuropathy, neurolymphomatosis, nerve sheath tumors, amyloidosis, sarcoidosis, and leprosy. With these diseases, other diagnostic testing is often insufficient, and specific histopathologic diagnosis can lead to disease-modifying treatment. Beyond these diseases, the utility of nerve biopsy overall is limited. In cases of ambiguous demyelinating and axonal polyneuropathies, histopathology often provides information already retrieved from electrodiagnostic testing.[35]

CONCLUSION

The initial clinical assessment of peripheral nerve diseases can be challenging because of nonspecific presentations. A careful history and examination that focuses on key clinical elements, with additional electrodiagnostic and laboratory evaluation, can differentiate between diverse causes of peripheral nerve diseases as well as diseases that extend beyond the peripheral nervous system. Although the available potential workup for peripheral nerve disease is broad, the practicing neurologist should focus and prioritize testing based on the initial clinical and electrodiagnostic assessment.

KEY POINTS

- **Imaging studies are most helpful when clinical suspicion for a specific diagnosis is high but electrodiagnostic testing results are ambiguous or inconclusive.**
- **Although neuromuscular ultrasound provides greater resolution of peripheral nerve anatomy, it is currently limited to the study of superficial nerves. The study of deeper (generally more proximal) peripheral nerves can be accomplished via MRI neurography.**
- **Nerve biopsy is most useful in cases of suspected vasculitic neuropathy and neurolymphomatosis. It can also be useful for the diagnosis of nerve sheath tumors, amyloidosis, sarcoidosis, and leprosy.**

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Guillain-Barré Syndrome

By Ali A. Habib, MD; Waqar Waheed, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: This article summarizes the clinical features, diagnostic criteria, differential diagnosis, pathogenesis, and prognosis of Guillain-Barré syndrome (GBS), with insights into the current and future diagnostic and therapeutic interventions for this neuromuscular syndrome.

LATEST DEVELOPMENTS: GBS is an acute, inflammatory, immune-mediated polyradiculoneuropathy that encompasses many clinical variants and divergent pathogenic mechanisms that lead to axonal, demyelinating, or mixed findings on electrodiagnostic studies. The type of antecedent infection, the development of pathogenic cross-reactive antibodies via molecular mimicry, and the location of the target gangliosides affect the subtype and severity of the illness. The data from the International GBS Outcome Study have highlighted regional variances, provided new and internationally validated prognosis tools that are beneficial for counseling, and introduced a platform for discussion of GBS-related open questions. New research has been undertaken, including research on novel diagnostic and therapeutic biomarkers, which may lead to new therapies.

ESSENTIAL POINTS: GBS is among the most frequent life-threatening neuromuscular emergencies in the world. At least 20% of patients with GBS have a poor prognosis and significant residual deficits despite receiving available treatments. Research is ongoing to further understand the pathogenesis of the disorder, find new biomarkers, and develop more effective and specific treatments.

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Address correspondence to Dr Waqar Waheed, 89 S Williams St, Burlington, VT 05401, waqar.waheed@uvmhealth.org.

RELATIONSHIP DISCLOSURE:
Dr Habib has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for the National Institutes of Health/National Institute of Neurological Disorders and Stroke and UCB S.A., and as a consultant for Pfizer Inc and in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, argenx, Genentech, Inc, Immunovant, Inc, and UCB S.A., and for serving on speakers bureaus for Alexion Pharmaceuticals, Inc, and argenx. The institution of Dr Habib has received research support from Alexion Pharmaceuticals, Inc, argenx, Cabaletta Bio, Inc, Genentech, Inc, Immunovant, Inc, Regeneron Pharmaceuticals Inc, and UCB S.A. Dr Waheed has received personal compensation in the range of $500 to $4999 for serving on a scientific advisory or data safety monitoring board for UCB S.A.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Habib and Waheed discuss the unlabeled/investigational use of IV immunoglobulin for the treatment of Guillain-Barré syndrome.

INTRODUCTION

Acute immune-mediated polyneuropathies are grouped under the umbrella term *Guillain-Barré syndrome* (GBS), which is one of the most common neuromuscular emergencies. GBS is a heterogeneous disorder that comprises several phenotypes, electrophysiologic features, and outcomes. This article discusses the clinical presentation, assessment, pathogenesis, and management of GBS.

EPIDEMIOLOGY

GBS is a rare, global disease with an incidence of 0.81 to 1.91 cases per 100,000 person-years in Europe and North America. Regional differences occur in the distribution of disease subtypes; demyelinating forms with a respiratory prodrome dominate in Europe and North America, whereas axonal subtypes with a preceding diarrheal illness are more common in Asia, particularly in Bangladesh and northern China.[1,2] Unlike other autoimmune diseases, GBS more

commonly affects men than women, and the incidence is higher in older age groups.[1,2]

Although several noninfectious factors including trauma, surgery, medications (including immune checkpoint inhibitors), and other systemic disorders have been reported as preceding the condition or as risk factors for the condition, infections are the most common antecedent event before the clinical development of GBS.[1] In case-control studies, *Campylobacter jejuni*, hepatitis E virus, cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae* have most consistently been associated with GBS.[3] Regional outbreaks of Zika virus–associated GBS in the mid-2010s occurred in French Polynesia, Latin America, and Caribbean countries.[4] In a study from south India, *C. jejuni*, dengue virus, and chikungunya virus were associated with GBS; however, the number of patients with GBS who were seropositive for chikungunya virus was much higher than those who were seropositive for *C. jejuni* (66.7% versus 32%), highlighting the difference in antecedent infection in tropical countries.[5]

A study that analyzed the first 1000 patients included in the International GBS Outcome Study for a recent infection with *C. jejuni*, hepatitis E virus, cytomegalovirus, Epstein-Barr virus, and *M. pneumoniae* led to some important observations.[6] *M. pneumoniae* was the most common preceding infection in children, and a higher percentage of demyelinating electrophysiologic features occurred with cytomegalovirus infection. Patients who tested positive for infection with *C. jejuni*, the most common infectious etiology (30% of all cases), had the most severe GBS presentations in all geographic areas. Although the distribution of infection was similar across geographic areas, the association between infection and clinical phenotype was different; the pure motor variant and axonal electrophysiologic subtype were more frequent in Asian compared with American or European cohorts. This finding suggests that the development of GBS may be influenced by immunogenetic variables in the host, such as variations in ganglioside distribution in nerve membranes or antibody binding ability. Microbial factors also play a role, such as differences in *C. jejuni* strains (Japan [strain O-19] and South Africa [strain O-41]),[7,8] and genetic polymorphisms in lipopolysaccharide biosynthesis genes in *C. jejuni* that modify ganglioside expression. Furthermore, this study also found subclinical infections in 28% of patients with GBS and a high frequency of coinfections (6%).[6] The latter point could point to true coinfections, which, if confirmed, would call for broad serologic testing, but it could also represent cross-reactive antibodies, particularly for flaviviruses, resulting from earlier flavivirus infection or vaccination. This is further demonstrated by the finding that all patients who were positive for dengue virus–specific IgM were also positive for other agents.[9]

Several cases resembling classic GBS, including typical therapeutic responsiveness, have been reported in close temporal association with COVID-19. However, a 2021 prospective cohort study and a 2022 retrospective epidemiologic study did not support any significant causal link between COVID-19 and GBS.[10,11] For more information, refer to the article "Infectious Neuropathies" by Aimee K. Boegle, MD, PhD, and Pushpa Narayanaswami, MD, FAAN,[12] in this issue of *Continuum*.

The more controversial issue has been the relationship between GBS and vaccinations. This association first came to light during the H1N1 epidemic of 1976 and again in 2009, creating widespread fears of vaccine-induced GBS.

Using surveillance data from the Centers for Disease Control and Prevention's Emerging Infections Program for the 2009 H1N1 pandemic, one study demonstrated a significantly lower cumulative risk of GBS in the vaccinated population compared with the unvaccinated population, indicating the benefit of vaccination.[13] Following the publication of several post–COVID-19 vaccine–associated GBS cases,[14] similar concerns exacerbated the public's existing reservations about different COVID-19 vaccines. A 2022 cohort study's interim analyses using surveillance data from the Vaccine Safety Datalink at eight participating integrated health care systems in the United States showed that the incidence of GBS in the 21 days after Ad.26.COV2.S was 32.4 per 100,000 person-years, which was substantially greater than the expected background rate of 1 to 2 per 100,000 person-years. GBS incidence in the 21 days after mRNA vaccination was 1.3 per 100,000 person-years, similar to the overall expected background rate. These results provided evidence that mRNA vaccines do not appear to be associated with GBS.[15] There are some conflicting data on the association of ChAdOx1 vaccine with GBS.[16-18]

Another study analyzed data from the US Vaccine Adverse Event Reporting System and found no increase in reporting rate following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination compared with the general population between December 2020 and October 2021, although the reporting rate was increased when comparing SAR-CoV-2 vaccination with other vaccinations.[19] These data alone should not be used to determine comparative safety among vaccine types, and it is important to consider other serious adverse events (eg, myocarditis and thrombosis with thrombocytopenia syndrome) that have also been associated with SARS-CoV-2 vaccines.[20]

In summary, research suggests that a causal relationship between COVID-19 vaccination and GBS has not been established for these vaccines, which supports the continuation of vaccination programs until there is clear, properly quantified evidence of increased GBS risk at a magnitude that outweighs the vaccination benefits.[21]

TERMINOLOGY BASED ON CLINICAL COURSE

A distinctive clinical course consisting of four phases is the key clinical hallmark of all GBS subtypes (FIGURE 2-1).[22,23] A prodromal phase is characterized by an antecedent event, which could be infectious or noninfectious, triggering a breakdown in immune tolerance and subsequent initiation of an immune-mediated process. This is followed by a progressive phase with the development of neuropathy symptoms, which by definition should not progress beyond 4 weeks. Symptoms typically reach a clinical nadir by 2 weeks; however, weakness can occasionally become established with an alarming speed, leading to respiratory failure requiring intubation within 12 to 24 hours of symptom onset. Patients then enter the plateau phase, which lasts for 1 to 4 weeks (median of 1 week), and subsequently enter the recovery phase, which can last several months.

More than 95% of patients with GBS experience a monophasic course, and less than 5% of cases have a documented recurrence.[24] Treatment-related fluctuations, defined as up to two relapses with worsening of at least one grade on the GBS disability scale or a decrease in the Medical Research Council (MRC) sum score, within 8 weeks of treatment initiation can occur in up to 10% of cases. Such treatment-related fluctuations often respond to re-treatment with the

KEY POINTS

- Demyelinating forms of Guillain-Barré syndrome (GBS) with a respiratory prodrome dominate in Europe and North America whereas axonal subtypes following a diarrheal illness are more common in Asia, particularly in Bangladesh and northern China.
- A small increased risk of GBS occurs after the Ad.26.COV2.S COVID-19 vaccine but not the mRNA vaccines.
- The GBS prodrome is followed by a progressive phase with the development of neuropathy symptoms, which by definition should not progress beyond 4 weeks.
- Treatment-related fluctuations can occur in up to 10% of patients with GBS and often respond to retreatment with the previously administered immunomodulatory therapy.

KEY POINT

- If a patient with an acute neuropathy has three or more relapses or progression beyond 8 weeks, then the diagnosis of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy should be considered.

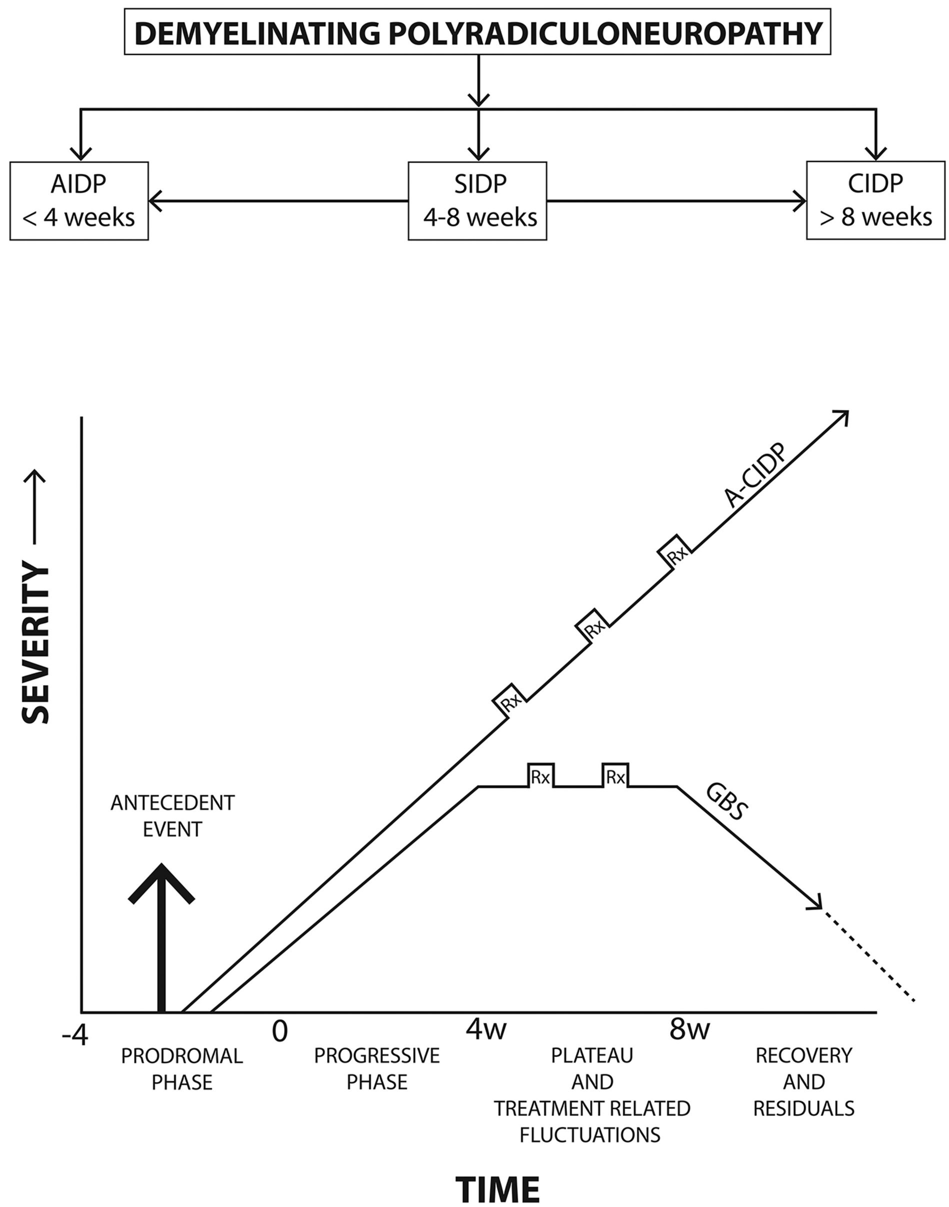

FIGURE 2-1
Clinical course of Guillain-Barré syndrome (GBS). The different subtypes of GBS fall on a continuum. In acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the progression is less than 4 weeks. Patients whose condition continues to worsen despite treatment may have acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP). In subacute inflammatory demyelinating polyradiculoneuropathy (SIDP), the progression is from 4 to 8 weeks. In typical CIDP, the progression is more than 8 weeks or with three or more fluctuations. Treatment-related fluctuations can occur in up to 10% of GBS cases.
Rx = treatment.

previously administered immunomodulatory therapy. Rapid pharmacokinetic clearance of intravenous immunoglobulin (IVIg) treatment leading to a shortened half-life is the potential explanation for IVIg-related treatment-related fluctuation.[25] However, in patients who have three or more relapses or progression beyond 8 weeks, the diagnosis of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) should be considered.[26] See the following section on treatment of patients whose condition worsens after initial improvement for details.

An intermediate subtype between GBS and CIDP, termed *subacute inflammatory demyelinating polyradiculoneuropathy*, has been described that reaches its nadir between 4 and 8 weeks. This represents a mixed group and requires careful follow-up as these patients are at risk of future relapses and evolution into CIDP and may require long-term immunosuppressive treatment.[27]

CLINICAL FEATURES

GBS can be classified based on neurophysiologic characteristics (axonal versus demyelinating forms) or clinical criteria because nerve conduction studies and CSF studies may be normal in the first week of symptom onset (FIGURE 2-2).

GBS has a wide range of clinical findings, indicating different degrees of involvement of motor, sensory, and autonomic nerve fibers along the spinal roots and cranial and peripheral nerves. TABLE 2-1 lists the core diagnostic criteria[28] of

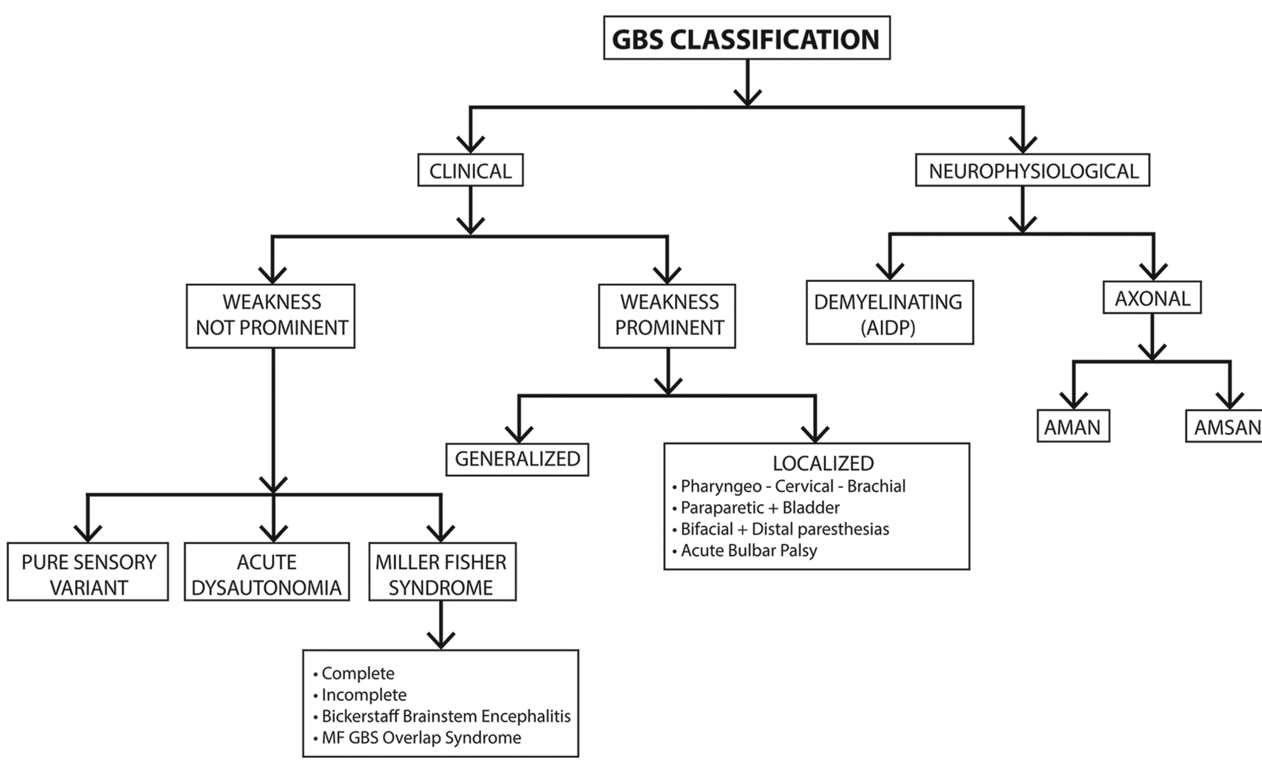

FIGURE 2-2

Clinical classification of Guillain-Barré syndrome (GBS). GBS classification is based on clinical and neurophysiologic features.

AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor-sensory axonal neuropathy; MF = Miller Fisher syndrome.

classic sensorimotor GBS, or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), representing the most common subtype in the United States and Europe (approximately 85% to 90% of cases).

Following an antecedent event, after a median interval of approximately 10 days, the earliest symptoms are distal paresthesia (acroparesthesia) and low back pain (due to nerve root inflammation), which are reported by approximately two-thirds of patients.[29] The presence of sensory symptoms helps exclude pure motor disorders such as motor neuron disease, myopathy, or myasthenia gravis; however, objective sensory loss is mild and delayed.

Since GBS is primarily a motor more than a sensory neuropathy, the main characteristic of classic GBS is the presence of symmetric weakness involving proximal and distal muscles. This is explained by the involvement of both proximal nerve roots and distal nerves (hence the term polyradiculoneuropathy), where the blood-nerve barrier is weak. An ascending pattern of weakness (legs earlier and weaker than arms) is more common than a descending presentation (onset in face and arms earlier than legs).

Weakness is accompanied by hyporeflexia or areflexia in approximately 90% of patients; however, this could be delayed by a week, while some patients with acute motor axonal neuropathy (AMAN) or Bickerstaff variants might have preserved reflexes or even hyperreflexia.[30]

Aside from limb weakness, involvement of cranial nerve-innervated muscles, particularly facial (50%), oropharyngeal (40%), and extraocular (ophthalmoplegia or ptosis in 5% to 15%) muscles, can occur; severe weakness of respiratory muscles, particularly the diaphragm, necessitates ventilatory support in 10% to 30% of patients with GBS.[31]

About two-thirds of patients have one or more autonomic abnormalities of variable severity. Although there are many variations since the sympathetic nerves are less myelinated, dysautonomia due to sympathetic hyperactivity

TABLE 2-1 **Diagnostic Criteria for Guillain-Barré Syndrome[a]**

Features required for diagnosis

- Progressive weakness of more than one limb
- Areflexia or hyporeflexia

Features that strongly support Guillain-Barré syndrome diagnosis

- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain
- Elevated CSF protein
- Characteristic electrodiagnostic features

CSF = cerebrospinal fluid.
[a] Data from Asbury AK and Cornblath DR, Ann Neurol.[28]

typically predominates in the acute phase, and parasympathetic failure is more prominent in the recovery phase.[24,25] These autonomic manifestations include cardiac arrhythmias (sustained sinus tachycardia is the most common abnormality); labile blood pressure (can rarely result in posterior reversible encephalopathy syndrome [PRES] or takotsubo cardiomyopathy from an excess of catecholamines); orthostatic hypotension from a lack of compensatory postural increase in sympathetic activity and vascular resistance in the splanchnic circulation, and disruption of baroreceptor reflexes; abnormal sweating; pupillary abnormalities; and gastrointestinal dysmotility and genitourinary dysfunction typically manifesting as paralytic ileus or urinary retention, which can mimic a spinal cord lesion by causing double incontinence and a pseudosensory level in 5% of cases.[24,25] Since dysautonomia can mimic other systemic problems such as early sepsis and may be accompanied by denervation hypersensitivity, it poses diagnostic and therapeutic challenges. Antihypertensive and antiarrhythmic medications should therefore be prescribed very cautiously, especially in older adults, since they have the potential to cause severe hypotension or aggravate arrhythmias.[32,33]

Uncommon clinical features in GBS include papilledema (associated with severely elevated CSF protein), facial myokymia, hearing loss, meningeal signs, and vocal cord paralysis.[34]

GUILLAIN-BARRÉ SYNDROME VARIANTS

Once thought to be a singular condition, based on clinical, pathophysiologic, and pathologic traits, GBS is currently acknowledged to be a diverse syndrome with several different variants: axonal variants, Miller Fisher syndrome, and localized variants.

Axonal Variants

Based on electrophysiologic data, axonal variants include AMAN (CASE 2-1) and acute motor-sensory axonal neuropathy (AMSAN). Apart from the involvement of the sensory nerves in patients with AMSAN, the two forms of the disease differ significantly. Both forms can be caused by a preceding *C. jejuni* infection. AMAN is more prevalent in Asia, is typically preceded by diarrhea, is more common in the summertime, and affects children more frequently.

In contrast, AMSAN has less of a geographic or seasonal pattern, is characteristically preceded by respiratory illness, and is more common in adults. Clinically, AMSAN is often more severe, with frequent autonomic and cranial nerve dysfunction. Muscle stretch reflexes in AMAN might be normal (probably because of sparing of the Ia afferents) or even exaggerated (because of dysfunction of spinal inhibitory interneurons).[30]

Based on pathophysiology, AMAN has two patterns of recovery: quick recovery within days of treatment may occur due to the resolution of conduction block (reversible conduction failure), or recovery may be slow and poor when associated with extensive axonal degeneration.[35,36] Once patients with AMAN are reevaluated and other causes excluded, instead of trying to combine immunotherapies or repeat IVIg, early supportive interventions and multidisciplinary rehabilitation are recommended. In contrast, AMSAN usually has an early nadir and protracted clinical course and is associated with severe residual disability.

KEY POINTS

- **Sensory symptoms help exclude pure motor disorders such as motor neuron disease, myopathy, or myasthenia gravis in patients with possible GBS; however, objective sensory loss is mild and delayed.**
- **Weakness is accompanied by hyporeflexia or areflexia in approximately 90% of patients with GBS; however, this finding may be delayed by up to a week, and some patients with acute motor axonal neuropathy might have normal or even exaggerated reflexes.**
- **Severe weakness of respiratory muscles, particularly the diaphragm, necessitates ventilatory support in 10% to 30% of patients with GBS.**
- **Acute motor-sensory axonal neuropathy is often clinically more severe than other variants of GBS, with frequent autonomic and cranial nerve dysfunction.**
- **Acute motor axonal neuropathy has two patterns of recovery: quick recovery within days because of the resolution of conduction block, or slow and poor recovery because of extensive axonal degeneration.**
- **Miller Fisher syndrome includes a spectrum of disorders with reactivity against specific antiganglioside GQ1b antibodies in approximately 85% to 90% of patients.**

Miller Fisher Syndrome

Miller Fisher syndrome includes a spectrum of disorders with serum antiganglioside GQ1b antibodies in approximately 85% to 90% of patients. The complete form of Miller Fisher syndrome is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia and is more common in East Asia, particularly in Japan.[1] Ataxia in patients with Miller Fisher syndrome arises either from cerebellar pathology (central) or from selective involvement of Ia afferent neurons along their path from muscle spindles to the spinal cord (peripheral).[37] Incomplete forms include acute ophthalmoplegia, acute ataxic neuropathy, acute ptosis, mydriasis, and acute vestibular syndromes.[38-40] Bickerstaff brainstem encephalitis is a Miller Fisher syndrome–related disorder in which patients develop impaired consciousness and paradoxical hyperreflexia in addition to ataxia and ophthalmoparesis due to the respective involvement of the reticular formation and pyramidal tracts. In Bickerstaff brainstem encephalitis, brain MRI abnormalities are present in only 30% of cases.[41]

Patients with features of Miller Fisher syndrome who develop limb weakness and respiratory insufficiency are characterized as having the Miller Fisher syndrome–GBS overlap syndrome.

CASE 2-1

A 32-year-old man with no significant past medical history presented to the emergency department for evaluation of diffuse limb weakness. Without any preceding illness, he had woken 2 days before with neck pain and a feeling of weakness in his upper and lower extremities. He had been unable to complete his routine workout but could still ambulate independently. On the day of presentation his weakness progressed to the point that he was unable to get out of a chair, necessitating an emergency evaluation.

Initial evaluation revealed no numbness, tingling, bowel or bladder incontinence, dysarthria, dysphagia, or exertional dyspnea; his mental status and cranial nerve examinations were normal. Neck flexion and extension strength were Medical Research Council (MRC) grade 4/5. Severe, symmetric upper and lower extremity weakness (MRC grade 3/5 proximally and 2/5 distally) and global areflexia were noted. Light touch, temperature, and vibration sensations were normal. Within a few hours, his weakness progressed to quadriplegia. CSF revealed 74 red blood cells/mm^3, 2 white blood cells/mm^3 (51% macrophages, 31% lymphocytes), normal glucose (66 mg/dL), and normal protein (28 mg/dL). He was diagnosed with acute motor axonal neuropathy (AMAN), and IVIg therapy was initiated. He developed progressive respiratory distress requiring intubation and mechanical ventilation on the second day of admission. Electrodiagnostic testing performed on day 14 from symptom onset confirmed a diagnosis of AMAN with absent compound muscle action potentials (CMAPs) in the right median, ulnar, peroneal, and tibial nerves, and normal sensory nerve action potentials. Needle EMG showed some increased insertional activity in the right

Localized Variants

These variants are characterized by the involvement of certain muscle groups or nerves and may not progress to a typical generalized phenotype. The variants include weakness limited to the cranial nerves (bilateral facial palsy with paresthesia or acute bulbar palsy); oropharynx, neck and shoulder muscles, sparing the lower limbs and thus mimicking botulism (pharyngeal-cervical-brachial variant); lower limbs, thus mimicking an acute spinal cord lesion (paraparetic variant); sensory nerves (pure sensory ataxic variant); and autonomic nerves (acute pandysautonomia). However, as these variants do not meet the diagnostic criteria for GBS, controversy exists over their inclusion as clinical GBS variants.[42]

PATHOGENESIS AND PATHOLOGY

The following factors are important in the immunopathogenesis of GBS.

Molecular Mimicry

Because of the similarities between the antigenic structures of pathogens and humans (molecular mimicry), humoral and T-cell–mediated immune responses are generated following an infection such as with *C. jejuni*, contributing to nerve

biceps and deltoid muscles; no volitional motor unit potentials were recorded in any upper or lower extremity muscles examined, and the right trapezius was normal. Repeat lumbar puncture on day 15 showed an increase in CSF protein to 63 mg/dL with normal glucose and cell count. Serum *Campylobacter jejuni* IgG antibody titer was elevated (1:1280; normal, <1:320). A serum antiganglioside antibody test was negative, and extensive workup for other causes was also negative. Because of a lack of significant improvement, tracheostomy and percutaneous endoscopic gastrostomy were performed on day 14, and he was transferred to a long-term acute care facility, where he showed a very gradual recovery.

COMMENT

This case highlights some important aspects of Guillain-Barré syndrome (GBS). While typically GBS symptoms reach a clinical nadir by 2 weeks, occasionally weakness can progress at an alarming speed requiring intubation and mechanical ventilation within a few days of onset. Once extensive axonal degeneration was documented and evaluation for other causes was unrevealing the diagnosis of AMAN was established. In this setting, early supportive interventions and multidisciplinary rehabilitation are recommended rather than combining or repeating immunotherapies.

This case also highlights the presence of subclinical infection in GBS, which in a recent study was found to be present in 28% of patients. Although antecedent infection testing does not alter care, it may offer valuable prognostic information.

KEY POINTS

- **The complete form of Miller Fisher syndrome, characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia, is more common in East Asia, particularly in Japan.**

- **Bickerstaff brainstem encephalitis is a Miller Fisher syndrome–related disorder, where, in addition to ataxia and ophthalmoparesis, patients develop impaired consciousness and paradoxical hyperreflexia because of involvement of reticular formation and pyramidal tracts.**

- **The localization of the target ganglioside antigens, as well as the binding specificity of the antiglycolipid antibodies, are associated with distinctive clinical subtypes of GBS.**

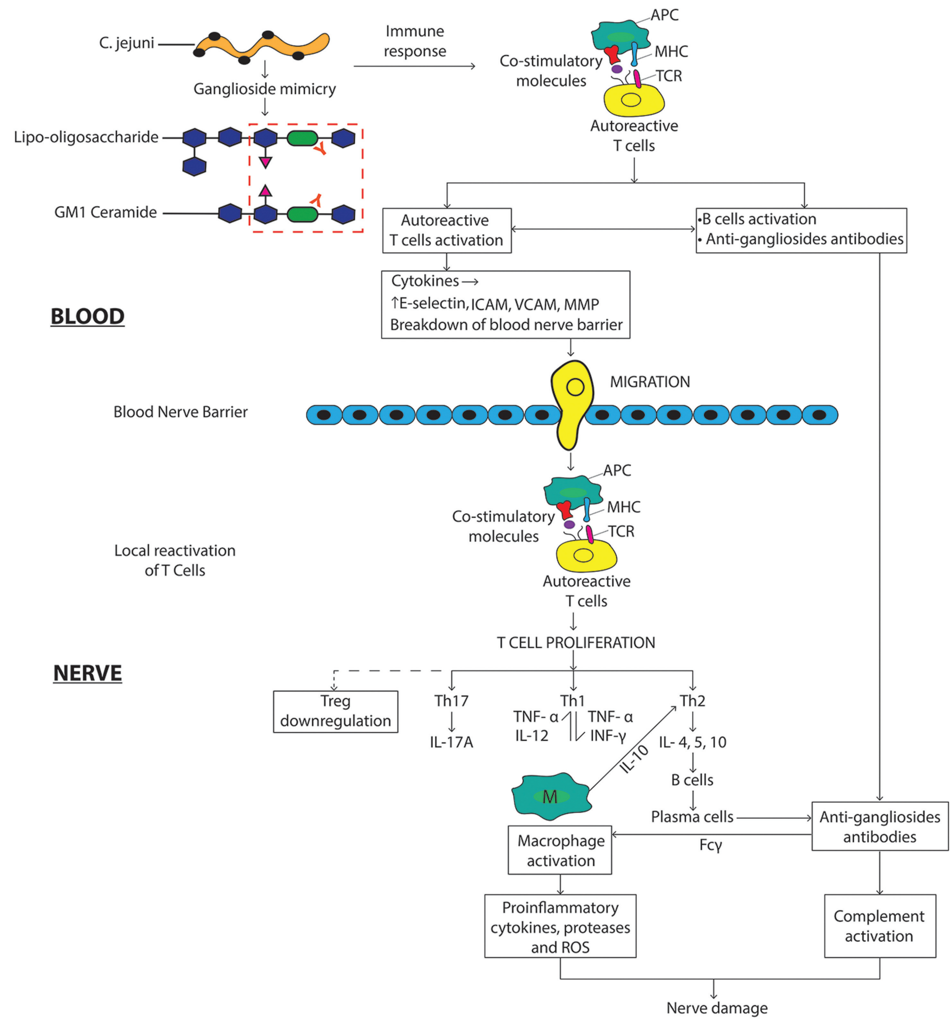

FIGURE 2-3

Different steps involved in Guillain-Barré syndrome (GBS) pathogenesis. (1) Antecedent infection leads to a cellular and humoral immune response generation against autologous targets via molecular mimicry. (2) Breakdown of the blood-nerve barrier. (3) Autoreactive T-cell proliferation, cytokine release, and antiganglioside antibodies production. (4) Recognition of antigenic targets and membrane attack complex formation. (5) Demyelination and axonal loss. (6) Macrophage invasion to remove debris.

APC = antigen-presenting cell; C. jejuni = *Campylobacter jejuni*; Fcγ = Fc gamma; ICAM = intercellular adhesion molecule; IFN-γ = interferon gamma; IL = interleukin; M = macrophage; MHC = major histocompatibility complex; MMP = matrix metalloproteinase; ROS = reactive oxygen species; TCR = T-cell receptor; Th1 = T helper 1; Th2 = T helper 2; Th17 = T helper 17; TNF-α = tumor necrosis factor α; Treg = regulatory T cells; VCAM = vascular cell adhesion molecule 1.

damage and GBS symptoms (FIGURE 2-3). These immune responses can be influenced by a combination of host and microbial factors; however, a potential role of genetic polymorphism, which confers susceptibility to GBS after an infection, requires further investigation.[43-45]

Neural Targets

The neural targets, especially in the axonal variants of GBS, are likely to be gangliosides that participate in receptor modulation, growth regulation, and

cell-cell interactions, particularly those between axons and glia. Their expression on the cell surface makes them potential antigenic targets for circulating components of the immune system.[46,47] The localization of these target ganglioside antigens as well as the binding specificity of the antiglycolipid antibodies have been associated with distinctive clinical subtypes of GBS (TABLE 2-2).[48,49]

Antiganglioside antibodies are not reliably present in all subtypes or patients with GBS. GM1 antibodies are common in axonal variants of GBS, particularly in those preceded by *C. jejuni* infection. The lipooligosaccharide molecules produced by *C. jejuni* strains linked to GBS frequently mimic the saccharide moieties of other gangliosides, including GM1a and GD1a.[47] Anti-GM1 and anti-GalNAc-GD1a antibodies are associated with motor abnormalities because GM1 and GalNAc-GD1a are mostly expressed on the axolemma of motor neurons, especially at the node of Ranvier of intramuscular motor nerve axons. GQ1b is strongly expressed in the extraocular muscles, muscle spindles, and reticular formation accounting for ophthalmoplegia, ataxia, and alteration of consciousness. The GQ1b antibody is thought to have a direct effect on the neuromuscular junctions between cranial nerves and ocular muscles. Dysphagia is explained by GT1a expression in the glossopharyngeal and vagal nerves.[50,51] IgG antibodies to moesin, which is located on Schwann cell microvilli at nodes and is associated with the rearrangement of plasma membrane flexibility, have been identified as a potential autoantigen in cytomegalovirus infection–related AIDP. Other studies have suggested the presence of IgG antibodies to myelin glycolipids such as galactocerebroside or LM1. In addition, IgG antibodies to neurofascin 155 or contactin-associated protein 1 have been detected in GBS sera associated with severe neuropathic pain, suggesting additional research into nodal and paranodal proteins as target antigens in GBS.[49]

Ganglioside Targets in Guillain-Barré Syndrome[a] TABLE 2-2

Guillain-Barré syndrome subtype	Target antigen
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	LM1, Gal-C
Acute motor axonal neuropathy (AMAN)	GM1, GM2, GD1b, GT1b, GM3, GD1a, GalNac-GD1a
Acute motor-sensory axonal neuropathy (AMSAN)	GM1, GM1b, GD1a
Bickerstaff brainstem encephalitis	GQ1b
Miller Fisher syndrome	GQ1b, GM1b, GT1a, GD3, GD1c
Pharyngeal-cervical-brachial variant	GT1a, GQ1b, GD1b
Sensory ataxic variant	GD1b

[a] Gangliosides nomenclature: Gangliosides are composed of a glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids (eg, *N*-acetylneuraminic acid) linked on the sugar chain. In their nomenclature, G stands for ganglioside, the second letter represents the number of sialic acid residues (M = 1, D = 2, T = 3, Q = 4), the numeral represents the number of neutral carbohydrates, and the lowercase letter (a/b) represents the isomeric position of sialic acid residue.

KEY POINTS

- In acute inflammatory demyelinating polyradiculoneuropathy, demyelination and multifocal perivascular and endoneurial T-cell infiltration ensue along the length of the nerve, particularly early in the proximal nerve roots and distal nerve segments where the blood-nerve barrier is weak.

- Acute motor axonal neuropathy is characterized by the presence of IgG anti-GM1 or anti-GD1a autoantibodies, which bind to the nodal axolemma, leading to complement activation and membrane attack complex formation.

Immunopathogenesis

The immune attack begins when tolerance is broken in the setting of infections such as *C. jejuni* (FIGURE 2-3). Gangliosidelike lipooligosaccharides expressed on *C. jejuni* are identified by antigen-presenting cells and induce proliferation of autoreactive T cells and the production of antimyelin glycolipid antibodies by B cells. Autoreactive T cells not only promote the production of autoantibodies by plasma cells but also secrete various cytokines that, via upregulation of adhesion molecules (eg, E-selectin, intercellular adhesion molecule, vascular cell adhesion molecule 1, and matrix metalloproteinase-9) on endothelial cells, facilitate the breakdown of the blood-nerve barrier to activated T cells, macrophages, and antimyelin antibodies. Local reactivation and clonal proliferation into T helper 1, T helper 2, or T helper 17 cells occur in the peripheral nervous system if these T cells encounter an endoneurial macrophage exhibiting autoantigenic epitopes and the necessary recognition molecules. By producing tumor necrosis factor-α and interferon gamma, T helper 1 cells help macrophages recognize Schwann cells whereas T helper 2 cells promote proliferation and differentiation of B cells. Inflammatory mediators, such as proinflammatory cytokines, reactive oxygen species, and proteases released by activated macrophages propagate the inflammatory response and directly damage the Schwann cells and axons leading to demyelination and secondary axonal degeneration (contact-dependent injury). In addition, downregulation of regulatory T cells, which maintain tolerance and suppress other immune cells such as B, T, and dendritic cells, also contributes to the immunopathogenesis of GBS.[52]

Antimyelin antibodies that cross the damaged blood-nerve barrier, or are produced locally by B cells that have been stimulated by T cells, also contribute to nerve damage by either complement-dependent (C3b receptor-dependent phagocytosis and membrane attack complex [MAC] formation) or complement-independent pathways by binding to the Fc gamma receptors on macrophages. Macrophage activation leads to the further release of toxic mediators and phagocytoses of myelin and myelin debris.[53]

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. Although autoantigens for the pathogenesis of AIDP have yet to be unequivocally identified, autoantibodies may bind to myelin antigens, activate complement to form MAC on the outer surface of Schwann cells, and initiate vesicular degeneration of myelin (FIGURE 2-4). Demyelination and multifocal perivascular and endoneurial T-cell infiltration ensue along the length of the nerve, particularly early in the proximal nerve roots and distal nerve segments where the blood-nerve barrier is weak. Demyelination blocks saltatory conduction along the nerves, accounting for sensorimotor deficits. Macrophages subsequently invade myelin and act as scavengers to remove myelin debris. After myelin has been cleared, Schwann cells depart the basal lamina of nerve fibers to produce offspring Schwann cells around demyelinated fibers to regenerate myelin. By encasing short portions of the fiber, these offspring Schwann cells produce short internodes within the current internode, which are distinct markers indicating earlier demyelination with subsequent remyelination. The short internodes are responsible for persistent conduction abnormalities seen in electrodiagnostic studies, even after good clinical recovery (see Electrodiagnostic Studies for additional details).[54]

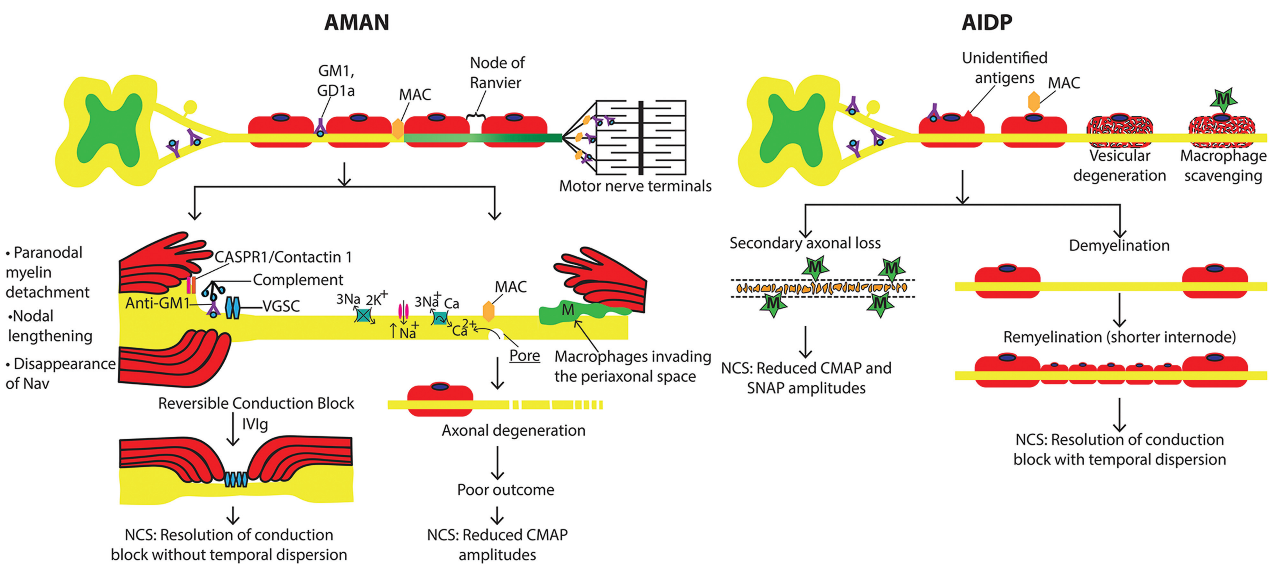

FIGURE 2-4

Pathologic and neurophysiologic correlation of Guillain-Barré syndrome (GBS). In acute motor axonal neuropathy (AMAN), specific gangliosides (GM1, GD1a) are targeted, which are located at nodal structures, ventral roots, and nerve terminals. Complement-mediated axonal conduction block from the loss of voltage-gated sodium channels and paranodal detachment could be reversible with treatment resulting in a prompt clinical recovery. However, intra-axonal calcium accumulation leading to axonal degeneration results in a poor outcome. In acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the antigenic targets are presumably located at the myelin sheath. A membrane attack complex (MAC) is formed as a result of complement activation leading to myelin destruction. Macrophages (M) then clear the debris. Intense inflammation leads to secondary axonal loss.
Ca = calcium; CASPR1 = contactin-associated protein-1; CMAP = compound muscle action potential; IVIG = intravenous immunoglobulin; K = potassium; Na = sodium; Nav = voltage-gated sodium channel; NCS = nerve conduction studies; SNAP = sensory nerve action potential.

Aside from the maintenance of rapid impulse propagation, several other crucial functions of myelinating Schwann cells maintain axonal integrity. These functions include mitigating energy consumption by creating the nodal architecture, regulating axon caliber by organizing axonal cytoskeleton networks, influencing mitochondrial distribution, providing trophic and possibly metabolic support, possibly supplying genetic translational materials, and safeguarding axons from toxic insults. The absence of these functions, particularly cytoskeletal organization in severe cases of AIDP, may trigger secondary axonal degeneration.[55]

ACUTE MOTOR AXONAL NEUROPATHY AND NODOPATHY. The antigenic targets in AMAN are located at nodal structures, ventral roots, and motor nerve terminals (FIGURE 2-4). The term *nodopathy* refers to the principal target areas in AMAN, the nodes of Ranvier, which are required to regenerate and propagate the action potential. At the nodes of Ranvier, where the voltage-gated sodium channels are located, gangliosides GM1 and GD1a are highly expressed.

AMAN is characterized by the presence of IgG anti-GM1 or anti-GD1a autoantibodies, which bind to the nodal axolemma, leading to complement activation and MAC formation. This leads to the disappearance of nodal sodium

channels and nodal lengthening. The extension of an autoimmune attack on the paranodal region destroys adhesion molecules (such as contactin and contactin-associated protein), leading to disruption of the axoglial junctions and detachment of the paranodal myelin terminal loop. Such a constellation of abnormalities results in inexcitable axolemma and nerve conduction block, causing muscle weakness. These changes can be reversible with treatment, resulting in the resolution of the conduction block (reversible conduction failure) and rapid reversal of weakness. However, in cases of intense immunologic activation, axonal degeneration may ensue, which explains the delayed recovery and poor outcomes seen occasionally in patients with AMAN. The axonal degeneration correlates with the intra-axonal accumulation of calcium from two potential mechanisms.[56] First, sodium/potassium pump inhibition caused by energy failure due to depletion of ATP results in an increase in axoplasmic sodium ions and axolemmal depolarization. Further sodium influx and buildup take place as a result of persistent sodium channel activation. Then, the function of the calcium/sodium exchanger is reversed, causing calcium ions to build up in the axoplasm. Second, MAC perforates the axolemma, resulting in pore formation via which calcium ions enter and accumulate in the axoplasm. The damaged axons are subsequently scavenged by macrophages that invade from the nodes into the periaxonal space (see the Electrodiagnostic Studies section for additional details).

AMSAN shares many similarities with AMAN, including paucity of inflammatory infiltration, although the attack in AMSAN is more severe and lasts longer, leading to more intense and ultimately widespread wallerianlike degeneration of both sensory and motor axons.

DIFFERENTIAL DIAGNOSIS

Diagnosis is relatively straightforward when a patient exhibits typical GBS symptoms, but the diagnosis can be challenging in patients with atypical presentations. Red flags suggesting a diagnosis other than GBS include the following[2,50]:

- **Severe respiratory dysfunction with limited limb weakness at onset**
- **Slow progression over 4 weeks without cranial nerve, autonomic, or respiratory involvement**
- **Severe sensory signs with limited weakness at onset**
- **Bladder or bowel dysfunction at onset**
- **Sharp sensory level on torso**
- **Marked persistent asymmetric weakness**
- **Fever at onset**
- **CSF pleocytosis (greater than 50 × 10/L), particularly if polymorphonuclear cells are prominent**

The differential diagnosis of GBS is large and depends on the clinical presentation, age, and geographic location of patients (TABLE 2-3).[51,57]

INVESTIGATIONS

The diagnosis of GBS rests on clinical characteristics, laboratory testing including CSF analysis, electrophysiologic studies, and occasionally radiologic investigations.

Laboratory Studies

All patients should undergo initial screening laboratory testing to rule out other potential reasons for sudden weakness, such as infections and metabolic or electrolyte disturbances. This includes a complete blood cell count, comprehensive metabolic profile, glycosylated hemoglobin, and thyroid function testing. Additional tests, such as vasculitic markers or toxicologic testing, may be required to investigate alternative reasons for abrupt-onset weakness, depending on the individual clinical presentation.

Testing for prior infections (eg, *C. jejuni*) might offer valuable epidemiologic data and may be a clue to prognosis, although such testing does not help with the diagnosis or change management of GBS.[58] A 2021 study has revealed a correlation between antibodies against combinations of gangliosides and various GBS variants, as discussed in the Pathogenesis section.[59] With a notable exception of the anti-GQ1b antibody, which is found in up to 90% of patients with Miller Fisher syndrome, the diagnostic value of other antiganglioside antibodies is limited, and assay dependent, and as such they are not recommended for routine testing. A negative test result does not rule out GBS, but a positive test result can be helpful, especially when the diagnosis is unclear, such as with an atypical presentation or in those cases with equivocal results on CSF analysis.[60,61]

CSF Analysis

The CSF examination is used not only to support the diagnosis of GBS but also to exclude other etiologies. Elevated total protein but normal cell count (albuminocytologic dissociation) is the most typical CSF abnormality in patients with GBS. This finding is explained by increased blood-nerve barrier permeability at the level of the proximal nerve roots. Protein levels might vary greatly, as they may be normal during the first week (up to 50% of patients) of the illness but increased in more than 90% of patients by the end of the second week.[1] According to a 2021 study, a high CSF protein level was linked with a demyelinating subtype and a severe disease course in the short term as measured by an inability to walk or run at week 2, but it did not add to the already established predictors for long-term outcomes.[62]

Mild CSF pleocytosis of 10 to 20 cells/mm^3 is seen in up to 5% of cases; however, the presence of marked pleocytosis of more than 50 cells/mm^3 should prompt evaluation for alternative causes. Given that IVIg therapy can raise CSF protein and white blood cell counts, CSF analysis following the start of IVIg therapy can be difficult to interpret.

Electrodiagnostic Studies

Electrodiagnostic studies (consisting of nerve conduction studies and needle EMG) based on the available electrophysiologic criteria[63-67] are performed to confirm the diagnosis, exclude mimics, offer prognostic data by differentiating between the axonal and demyelinating subtypes, and estimate the extent and location of axonal loss.

For the accurate electrodiagnosis of GBS subtypes, patients may require two studies between 1 and 3 weeks apart. The initial study assists in validating the diagnosis of acute neuropathy and is occasionally nonspecific or normal when performed very early in the course of the illness, when patients have initial proximal weakness only, or if the disease is very mild. The second study refines

KEY POINTS

- Mild CSF pleocytosis of 10 to 20 cells/mm^3 is seen in up to 5% of patients with GBS. The presence of marked pleocytosis of more than 50 cells/mm^3 should prompt the evaluation for alternative causes.
- Given that intravenous immunoglobulin (IVIg) therapy can raise CSF protein and white blood cell counts, CSF analysis following the start of IVIg therapy can be difficult to interpret.
- Electrodiagnostic studies performed early in the course of GBS may be normal or show subtle or nonspecific abnormalities. Often, a repeat study performed several weeks later is required for definitive characterization of the disease subtype.

the subtype classification and approximates the extent of any axonal loss, which helps with the prognosis.

Findings in demyelinating variants of GBS (FIGURE 2-4 and FIGURE 2-5A[68]) include early prolonged-latency or absent F waves and absent H reflexes, reflecting involvement of proximal nerve trunks or roots; increased distal latency and conduction block with temporal dispersion in motor nerves (prolonged distal compound muscle action potential [CMAP] duration of more than 8.5 ms seen in 65% with 98% specificity)[69]; reduced motor conduction velocities that are not seen until the third or fourth week of illness (an indication of conduction slowing as a sign of remyelination producing short internodes); and reduced recruitment (early) or fibrillation potentials (after several weeks) on

TABLE 2-3 **Differential Diagnoses in Guillain-Barré Syndrome**

Presentation	Differential diagnosis
Pure motor presentation Guillain-Barré syndrome (GBS) is predominantly a motor more than sensory neuropathy; however, in the absence of sensory symptoms such as in acute motor axonal neuropathy (AMAN), pure motor disorders need to be considered and excluded by appropriate testing	Infectious motor neuronopathies (West Nile virus, enteroviruses particularly in children, rabies and polio in pertinent geographic areas), myopathies, neuromuscular junction disorders (autoimmune, botulism, or from consumption of various plants such as hemlock or exposure to snake bites [eg, cobra or krait]), acute hypokalemic and thyrotoxic periodic paralysis, hypermagnesemia, acute predominantly motor neuropathies such as porphyria (upper limb predominance; abdominal, psychiatric, and autonomic symptoms) and lead toxicity (radial neuropathy with involvement of wrist and finger extensors), toxicity with organophosphates (eg, exposure to pesticides or plastics and petroleum manufacturing)
Paraparesis, spinal sensory level, or bowel and bladder dysfunction at onset Differential diagnosis in patients with the paraparetic variant of GBS should be considered	Spinal cord or cauda equina compression or spinal cord infarction, transverse myelitis
Asymmetric weakness Patients with GBS typically have symmetric sensorimotor deficits; in the setting of asymmetric weakness, the differential diagnoses need to be expanded accordingly	Vasculitic neuropathy (painful sensorimotor deficits in the distribution of individual peripheral nerves, involvement of other organs), multiple mononeuropathies, infections (eg, Lyme disease, [history of exposure and characteristic rash, ie, erythema migrans, in Lyme disease] diphtheria [following laryngeal infection] or poliomyelitis), leptomeningeal malignancy (eg, carcinomatosis or lymphomatosis [known cancer; headaches, encephalopathy, and multiple cranial neuropathies in leptomeningeal lymphoma])
Cranial neuropathies including ophthalmoplegia and bulbar dysfunction The differential diagnosis of anti-GQ1b antibody–associated GBS variants (Miller Fisher syndrome, Bickerstaff brainstem encephalitis, bulbar palsy) and pharyngeal-cervical-brachial subtype can mimic various conditions	Brainstem stroke (hyperacute onset), myasthenia gravis (fatigable weakness), botulism (pupillary abnormalities, dysautonomia, and descending paralysis), Wernicke encephalopathy (predisposing factors including alcoholism, prior gastric bypass surgery, hyperemesis gravidarum, and malnutrition), other etiologies for rhombencephalitis (infective, inflammatory, or infiltrative), and rarely, Lambert-Eaton syndrome (proximal weakness, areflexia, and dysautonomia)

CONTINUED ON PAGE 1343

needle EMG of weak muscles, especially when associated with secondary axonal loss.

A sparing pattern with preserved sural sensory nerve action potential (ie, "sural sparing" when the upper limb sensory responses are either absent or reduced [seen in 16% with 98% specificity])[70] suggests non–length-dependent neuropathies and also strengthens the suspicion for GBS. Additional studies, such as prolongation of blink reflex latencies, may be helpful with the bulbar-predominant presentation of GBS or when limb responses are absent.[71]

In AMAN, two patterns of conduction abnormalities are seen in serial studies. First, stable or worsening distal CMAP amplitudes with relatively preserved sensory amplitudes, distal motor latencies, and conduction velocities suggesting

CONTINUED FROM PAGE 1342

Presentation	Differential diagnosis
Severe diaphragmatic weakness with limited limb weakness at the onset When the severity of respiratory muscle weakness is disproportionate to limb weakness, the differential diagnosis should expand accordingly	Myasthenia gravis, high cervical cord intramedullary lesions (eg, tumor, abscess, inflammatory disease), Pompe disease, botulism, hypermagnesemia, or hypophosphatemia
CSF pleocytosis (>50 × 10/L) In patients with an elevated CSF cell count, the differential diagnosis should be considered and excluded by appropriate testing	Infections, particularly due to cytomegalovirus, human immunodeficiency virus (HIV), Lyme disease, polio virus; inflammatory disorders (eg, transverse myelitis); infiltrative disorders (eg, leptomeningeal carcinomatosis or lymphomatosis)
Other acute polyneuropathies Many polyneuropathies might resemble GBS by exhibiting sudden onset of symptoms	Critical illness polyneuropathy; toxic neuropathies such as those due to arsenic (environmental exposure, abdominal pain, Mee lines); thallium (alopecia), tetrodotoxin (from consuming incorrectly prepared raw puffer fish [fugu], a Japanese delicacy); plants (eg, buckthorn); n-hexane (eg, glue sniffing or occupational exposure); tick paralysis (asymmetric limb or bulbar weakness in children with normal CSF and quick recovery following removal of embedded tick); paraneoplastic polyneuropathies (often with a known systemic cancer and additional neurologic manifestations such as encephalopathy)
Sensory ataxia Differential diagnosis of the rare sensory ataxic variant of GBS differs from the typical motor-predominant subtype	Paraneoplastic ganglionopathy, Sjögren syndrome, pyridoxine toxicity, chemotherapy-induced polyneuropathy (eg, vincristine, cisplatin, carboplatin, taxanes)
Bifacial weakness The differential diagnosis in the bifacial variant of GBS is distinct from other subtypes	Infections (eg, Lyme disease, HIV infection); inflammatory (eg, sarcoidosis, meningitis [neoplastic or infectious], bilateral Bell's palsy, Melkersson-Rosenthal syndrome [facial palsy, granulomatous cheilitis, and fissured tongue])

CSF = cerebrospinal fluid.

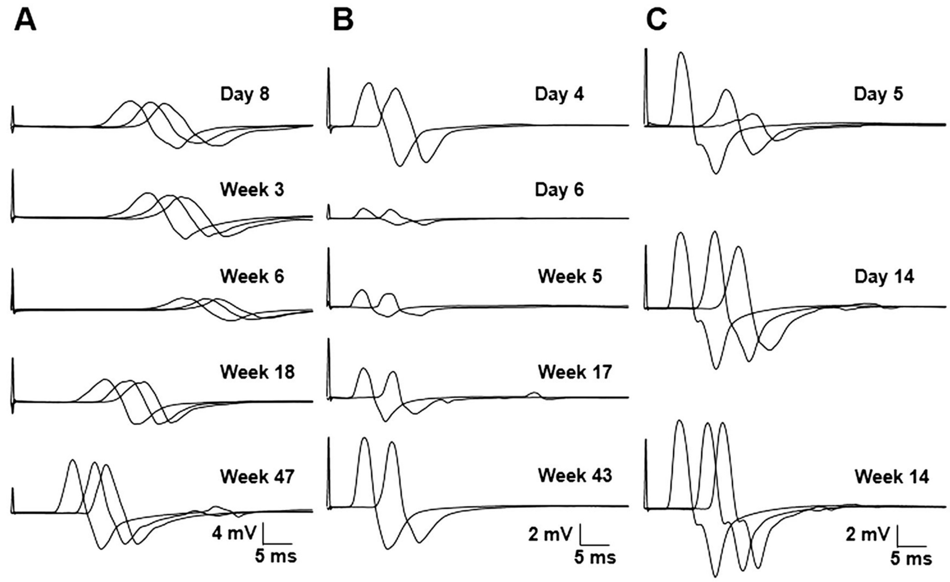

FIGURE 2-5
Electrodiagnostic findings in Guillain-Barré syndrome (GBS). Superimposed compound motor action potential (CMAP) recordings over the abductor pollicis brevis muscle, following stimulation of the median nerve at the wrist and elbow. *A*, Acute inflammatory demyelinating polyradiculoneuropathy demonstrating prolongation of distal latencies, CMAP temporal dispersion, and loss of CMAP amplitude culminating at week 6 with subsequent recovery. *B*, Acute motor axonal neuropathy (AMAN) demonstrating severe loss of CMAP amplitude culminating at day 6 with subsequent recovery and relative sparing of distal latencies and conduction velocities and no temporal dispersion. *C*, Acute motor-conduction-block with conduction blocks noted in the median nerve between wrist, forearm, and upper arm segments seen on day 5 with subsequent improvement in conduction blocks.
Reprinted with permission from Bae JS, et al, J Neurol Neurosurg Psychiatry.[68] © 2014 BMJ Publishing Group Ltd.

axonal degeneration, lack of temporal dispersion, and F-waves that may be absent but are not significantly prolonged in latency (FIGURE 2-4 and FIGURE 2-5B[68]). Second, low-amplitude distal CMAPs or abnormally reduced CMAP amplitude between two sites of stimulation that rapidly resolves on serial conduction studies, without excessive temporal dispersion or conduction slowing, indicates reversible conduction block and is associated with prompt clinical recovery (FIGURE 2-4 and FIGURE 2-5C[68]). If distal reversible conduction failure is not recognized as the cause of decreased distal CMAP amplitudes in a single test, an incorrect diagnosis of axonal degeneration may be made, with an incorrect conclusion of poor prognosis.[72]

Both CMAP and sensory nerve action potential (SNAP) amplitudes are reduced in the AMSAN variant of GBS. Interestingly, reversible conduction failure restricted to sensory nerves (in the sensory ataxic variant and Miller Fisher syndrome) and to both motor and sensory nerves (in AMSAN and pharyngeal-cervical brachial variant of GBS) has also been identified.[73]

Neuroimaging

MRI of the neuraxis with contrast enhancement is an emerging tool but is not a part of the routine diagnostic evaluation of GBS. MRI can be helpful in

diagnosing GBS in the presence of red flags, identifying certain GBS variants such as the Miller Fisher syndrome and the pharyngeal-cervical-brachial and paraparetic variants, and excluding mimics including brainstem infection, stroke, myelopathy, or cauda equina syndrome. Spinal MRI scans can reveal thickening or enhancement of the intrathecal spinal nerve roots and cauda equina with a sensitivity of 83%, supporting a diagnosis of GBS, especially in young children in whom clinical and electrophysiologic examinations can be difficult.[29,74] Similarly, enhancement of cranial nerves or posterior columns has been described in cases of Miller Fisher syndrome.[75,76]

Peripheral nerve ultrasound may show enlarged cervical nerve roots early in the disease course, with progressive improvement of their cross-sectional area on serial studies performed during the recovery phase. Moreover, additional features such as sparing of sensory nerves and transient enlargement of nerve roots or the vagus nerve may help differentiate GBS from acute CIDP, with a positive predictive value of more than 85%.[77] Normalization of nerves on ultrasound studies, assessed 6 months from onset, may provide additional support for the diagnosis of GBS.[78]

EMERGING INVESTIGATIONS

Several recently developed technologies and biomarkers can help differentiate between the GBS subtypes. Some of these markers available on a research basis include levels of soluble receptor for advanced glycation end products, an integrative metabolomic approach using CSF samples as well as plasma lipid metabolites and cytokines and T-cell ratios.[79-83]

TREATMENT

Treatment of GBS includes both supportive and disease-specific interventions.

Supportive care

Supportive care is the cornerstone of GBS management. A summary of pertinent clinical interventions, their evaluation, and the pathophysiology of neuromuscular respiratory failure in GBS is summarized in FIGURE 2-6.[84,85]

PATIENT TRIAGE AND ASSESSMENT OF VENTILATION STATUS. The presence of one or more of the following factors[84-86] should prompt consideration of admission to the intensive care unit (ICU): dysautonomia, bulbar dysfunction, severe or rapidly worsening weakness (based upon the time between the onset of weakness and presentation, particularly affecting neck and hip flexors),[87] and evolving respiratory distress. Respiratory status is assessed by clinical bedside evaluation (FIGURE 2-6) such as respiratory rate; recruitment of accessory respiratory muscles; counting during the expiration phase after a single full-capacity inspiratory breath (the inability to count to 15 or more during a single breath predicts a subsequent need for mechanical ventilation); and diminished strength of cough. In addition, the “20/30/40 rule” can be applied to bedside pulmonary function tests: the patient is deemed at risk for respiratory failure if the vital capacity is <20 mL/kg, the maximum inspiratory pressure is <30 cm H_2O, or the maximum expiratory pressure is <40 cm H_2O. These parameters should be monitored every 2 to 4 hours in all patients with GBS in the acute setting; a rapid decline in respiratory function (>30% in 24 hours) should also prompt admission to the ICU. For patients with mild weakness who

KEY POINTS

- Spinal MRI can demonstrate thickening and enhancement of intrathecal spinal nerve roots, supporting a diagnosis of GBS with a sensitivity of 83%, especially in young children in whom clinical and electrophysiologic examinations can be difficult.
- The following factors may prompt admission of patients with GBS to the intensive care unit: dysautonomia, bulbar dysfunction, severe or rapidly worsening weakness, and evolving respiratory distress.
- A score of more than 4 on the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score suggests a high (≥65%) risk of respiratory failure, which warrants monitoring in an intensive care setting.

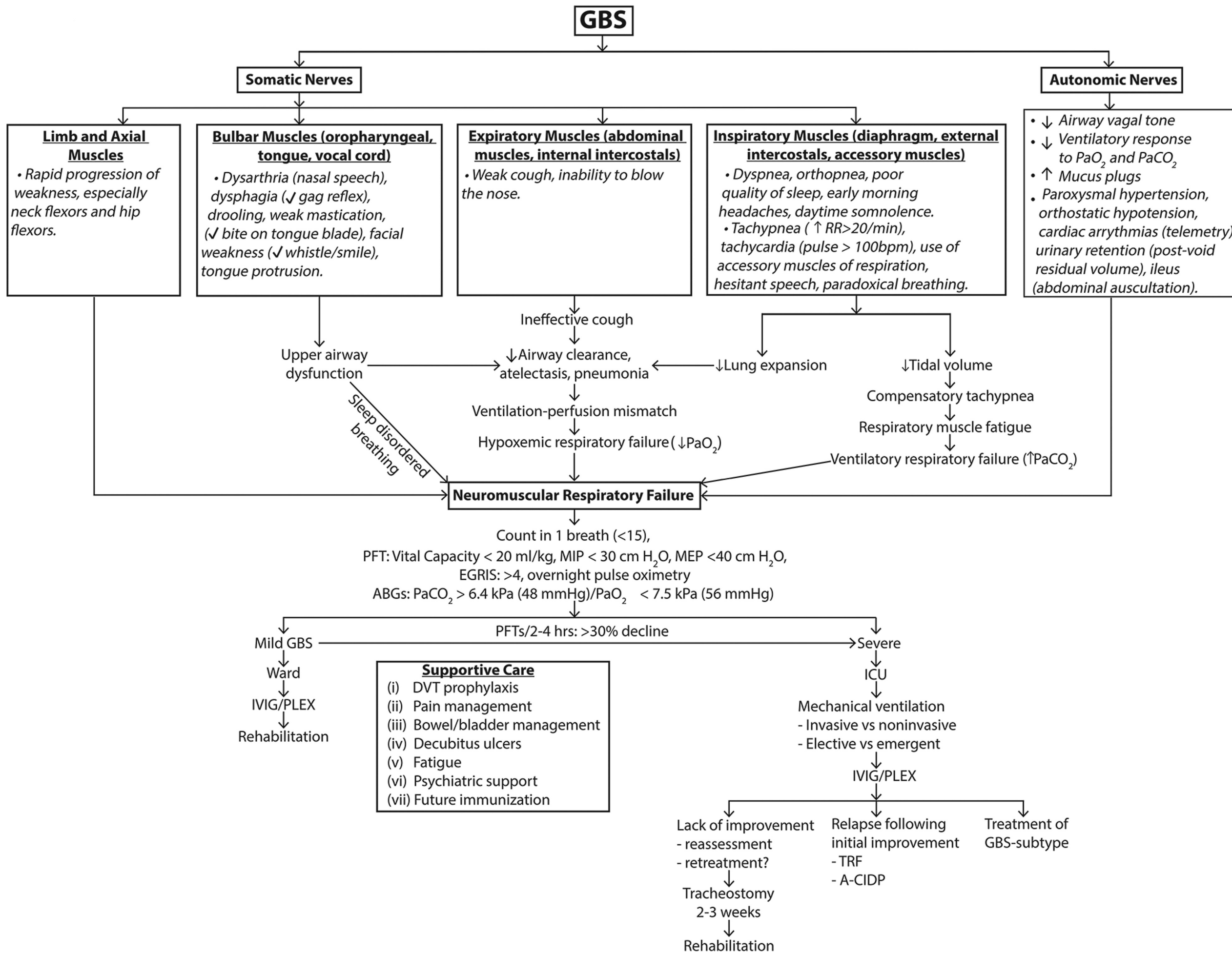

FIGURE 2-6

Neuromuscular respiratory failure in Guillain-Barré syndrome (GBS).

A-CIPD = acute-onset chronic inflammatory demyelinating polyradiculoneuropathy; ABG = arterial blood gas; DVT = deep vein thrombosis; EGRIS = Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score; ICU = intensive care unit; IVIG = intravenous immunoglobulin; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; PFT = pulmonary function testing; PLEX = plasma exchange; RR = respiratory rate; TRF = treatment-related fluctuation.

maintain clinical stability for at least 2 to 3 days, the frequency of monitoring can be decreased to every 6 to 8 hours.

The Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score (EGRIS) at the time of admission can also be used to predict the risk of respiratory failure within the first week of hospitalization; a score of more than 4 suggests a high (≥65%) risk of respiratory failure, thus prompting admission to the ICU (see the Prognosis section for details).[88]

Findings from a 2023 study concluded that the inclusion of MRC scores for selected proximal muscles, including neck and hip flexors, provided equal discriminative ability as the MRC sum score and might serve as a simplified tool for assessing respiratory insufficiency.[89]

Not all patients with GBS warrant admission to the ICU; those who have reached a clinical nadir or have experienced a modest decline over days with continued ambulation may be treated on the general ward with continuous monitoring.

MECHANICAL VENTILATION. Mechanical ventilation is required for 10% to 30% of all patients with GBS and is indicated in the presence of signs of impending respiratory failure. These include the presence of at least one major criterion (hypercarbia indicated by the partial pressure of arterial carbon dioxide >6.4 kPa [48 mm Hg], hypoxemia indicated by a partial pressure of arterial oxygen while the patient is breathing ambient air of <7.5 kPa [56 mm Hg], and a vital capacity <15 mL/kg of body weight) or two minor criteria (weak cough, impaired swallowing, and atelectasis). Ultimately, intubation is a clinical decision made at the patient's bedside. Intubation should ideally be elective, as emergency intubation can provoke dramatic blood pressure shifts and profound bradycardia by the introduction of an endotracheal tube in patients with dysautonomia. Additional safety precautions during intubation include the use of topical anesthesia, fiber optic laryngoscopy to assist intubation, short-acting benzodiazepines for sedation, and the avoidance of the use of depolarizing neuromuscular blockers (such as succinylcholine), which can provoke potentially fatal hyperkalemia owing to heightened chemosensitivity of denervated muscles.[90,91]

As patients with GBS would have already entered the progressive phase of the illness by the time respiratory muscle weakness ensues and is unlikely to reverse quickly, temporary intervention with noninvasive ventilation, especially in the presence of bulbar dysfunction, is not recommended. Moreover, noninvasive ventilation use might increase the likelihood of emergency intubation and aggravation of dysautonomia.[90,91]

OTHER SUPPORTIVE MEASURES. Patients with GBS need multidisciplinary supportive care to receive symptomatic treatment and prevent systemic complications (FIGURE 2-6). Physical therapy, occupational therapy, speech therapy, nutritional support, social services, and occasionally psychiatric support should be involved early.

Routine vaccinations after GBS are advised due to the low risk of GBS triggered by vaccine administration (one to two additional cases of GBS per million people vaccinated), which is significantly lower than the overall health risk posed by an infection-related illness. Additionally, vaccination may reduce the risk of GBS that may be triggered by infection (see the Epidemiology section for details). However, routine immunization is avoided in the acute phase and may be postponed for a few months due to the possibility that immunotherapies for GBS may impair the immunologic response to vaccination. Future avoidance may be considered when GBS manifests within 6 weeks after receiving a particular vaccination. For patients with a history of GBS, mRNA COVID-19 vaccines can be considered because of the potential increased risk of GBS linked with the Ad26.COV2.S COVID-19 vaccine.[50]

Immunotherapy

IVIg and plasma exchange have proven to be effective in multiple trials for the treatment of GBS.

KEY POINTS

- Patients with GBS who have reached a clinical nadir or have experienced a modest decline over days with continued ability to ambulate may be treated in the general ward with continuous monitoring.
- Intubation of patients with GBS and respiratory decline should be performed electively when possible, as emergency intubation can provoke dramatic blood pressure shifts and profound bradycardia by the introduction of an endotracheal tube in patients with dysautonomia.
- Noninvasive ventilation is usually insufficient for patients with GBS and respiratory decline and raises the risk of emergency intubation and aggravation of dysautonomia.
- Clinical trials have shown that IVIg and plasma exchange are effective in reducing the time to recovery in patients with GBS who are unable to walk a distance of 10 meters independently.

INDICATIONS AND TIMING TO INITIATE IMMUNOTHERAPY. Clinical trials have shown that IVIg and plasma exchange, when started within 2 and 4 weeks, respectively, of the onset of weakness are effective in reducing the time it takes for 40% to 50% recovery to begin in patients with GBS who are unable to walk a distance of 10 meters independently. Furthermore, a Cochrane analysis of plasma exchange for the treatment of GBS revealed that plasma exchange shortened the time on a ventilator, and the proportion of ventilator-dependent participants was significantly decreased.[92] Neither IVIg nor plasma exchange stops the progression of the disease or changes the degree of nerve damage. Given that the therapeutic advantages of plasma exchange were greatest in patients 1 week after the initiation of treatment, an early course of treatment with immunotherapy is preferred to minimize endoneurial inflammation and nerve injury.[92,93]

Although evidence from controlled trials is lacking, treatment should be considered for "mildly affected" ambulatory patients especially if they display rapidly progressive weakness or autonomic, bulbar, or respiratory involvement.[94]

SELECTION OF IVIG VERSUS PLASMA EXCHANGE. While both therapies are equally effective, the choice between plasma exchange and IVIg is dependent on local availability, patient preference, cost, risk factors, and contraindications. In general, IVIg is preferred due to its better tolerability and ease of administration.

IVIg is administered at a dose of 0.4 g/kg daily for 5 consecutive days, or 1 g/kg daily for 2 days; one study showed that children receiving therapy for 2 days as opposed to 5 days more commonly had treatment-related fluctuations.[95] Adverse effects include transfusion reactions, headache with or without aseptic meningitis, rash, acute hyperosmolar kidney injury (from sucrose-containing IVIg products), thromboembolism from hyperviscosity, and rarely IgA deficiency–related anaphylaxis.

Plasma exchange (200-250 mL plasma/kg body weight) is typically administered during five sessions over 10 days. One study found that two plasma exchange sessions were beneficial for patients who could walk with or without assistance but could not run; at least four exchanges were necessary for individuals who were more severely affected.[96] Complications of plasma exchange include hypotension, sepsis, transfusion reactions, thrombocytopenia, impaired clotting parameters, hypocalcemia, and issues with IV access. Early studies revealed that plasma exchange had a higher discontinuation rate than IVIg.[92]

TREATMENT OF PATIENTS WITH NO RESPONSE TO INITIAL IMMUNOTHERAPY. A therapeutic challenge arises in up to 40% of patients[93] who report no clinical improvement after reaching a plateau (at about 4 weeks) following initiation of immunotherapy, even when alternative etiologies have been reassessed and excluded. Two approaches have been studied: (1) combination therapy (plasma exchange followed by IVIg[97] or IVIg followed by plasma exchange, although the latter approach could be counterproductive by removing the previously administered immunoglobulins); or (2) retrial with a second course of IVIg.[98] These interventions either provide no additional benefit or are fraught with more adverse effects. The pathobiology in these patients

might represent a severe or prolonged immune attack leading to severe axonal degeneration. Further, lack of early improvement may not necessarily indicate that the treatment is ineffective, as progression could have been worse without therapy. Early supportive interventions are recommended in these patients, including percutaneous endoscopic gastrostomy if needed, tracheostomy (performed after at least 2 weeks of artificial ventilation if pulmonary function testing does not demonstrate sufficient improvement), and ultimate discharge to a rehabilitation facility.

TREATMENT OF PATIENTS WHOSE CONDITION WORSENS AFTER INITIAL IMPROVEMENT WITH IMMUNOTHERAPY. This group may represent patients with treatment-related fluctuations or acute-onset CIDP and frequently responds either to retreatment with the previously administered immunomodulatory therapy (treatment-related fluctuations) or long-term immunosuppressive medications (acute-onset CIDP). While the electrophysiologic findings are similar in these groups, patients with acute-onset CIDP are less likely to have autonomic nervous system involvement, facial weakness, a preceding infectious illness, or need for mechanical ventilation. Prominent sensory signs (rather than symptoms, which are common in AIDP) including impaired vibration and proprioception sensations leading to sensory ataxia, favor a diagnosis of acute-onset CIDP.[26]

TREATMENT IN GUILLAIN-BARRÉ SYNDROME SUBTYPES. Data from controlled trials are lacking on the best management of the different subtypes of GBS. Results from a small trial, albeit with methodologic limitations, suggested that the AMAN subgroup had better outcomes with plasma exchange than IVIg and that plasma exchange represented the most cost-effective option for this GBS subtype.[99] A 2022 retrospective study compared the outcomes of patients with GBS treated with IVIg to the disease's natural course, and discovered that IVIg was beneficial for AIDP but not for AMAN subtypes.[100] Prospective controlled trials are required to confirm these observations.

Most patients with pure Miller Fisher syndrome experience a mild course that resolves completely in 6 months without treatment. In these cases, withholding treatment seems reasonable, but close monitoring and immunotherapy may be warranted for patients who experience progressive spread to limb, cranial, or respiratory muscles.[94]

Since the effectiveness of immunotherapy in treating less common variants of GBS is not yet proven, decisions about acute treatment are made based on the severity of the symptoms and the overall clinical context.[101]

Corticosteroids

Although it is expected that corticosteroids should help reduce inflammation, and consequently disease progression in GBS, eight randomized controlled trials on the efficacy of corticosteroids in GBS have revealed no significant benefit, and treatment with oral corticosteroids has a detrimental impact on clinical outcomes.[102]

PROGNOSIS

Following GBS, functional recovery takes several weeks, and the degree of improvement varies based on individual risk factors.

KEY POINTS

- **Repeating IVIg or plasma exchange for absence of clinical response after initial treatment for GBS provides no additional benefit.**

- **While the electrophysiologic findings are similar between acute inflammatory demyelinating polyradiculoneuropathy and acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), patients with acute-onset CIDP are more likely to have sensory deficits or ataxia and less likely to have had a preceding infectious illness, autonomic nervous system involvement, facial weakness, or need for mechanical ventilation.**

- **Two validated prognostic models, the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score and modified Erasmus GBS Outcome Score, are available in a user-friendly online version to guide the need for mechanical ventilation within a week of admission and the functional outcome of patients with GBS at 6 months, respectively.**

Predictors of Need for Mechanical Ventilation and Long-term Functional Outcome

Two validated prognostic models, EGRIS and modified Erasmus GBS Outcome Score systems, are available in a user-friendly online version (gbstools.erasmusmc.nl) to predict the need for mechanical ventilation within a week of admission, and the functional outcome at 6 months, in patients with GBS.[84,103] EGRIS incorporates the time from onset of weakness to hospitalization, presence or absence of facial or bulbar weakness at admission, and MRC scores at admission to predict the risk of respiratory failure within the first week of hospitalization. The scale is scored from 0 to 7; higher scores indicate higher risk. The modified Erasmus GBS Outcome Score uses data at the time of hospital admission, or 1 week after admission, to predict the probability of being able to walk independently at 1, 3, and 6 months. It incorporates the patient's age, presence or absence of preceding diarrhea, and the MRC sum score to create scores from 0 to 12; higher scores indicate higher risk.

Overall, the long-term outcome of GBS is favorable; approximately 80% of patients can walk independently, and more than half recover fully after 1 year.[104] However, persistently low-amplitude CMAPs suggestive of axonal loss on electrodiagnostic studies are considered a poor prognostic factor, where recovery may continue well beyond the 1-year mark and could be incomplete.[105]

Residual Deficits

Despite immunomodulatory treatment, residual features such as weakness, paresthesia, fatigue, and pain can persist after 1 year, impacting the patient's daily activities and quality of life. Importantly, in one study 32% of patients had to change their work because of GBS.[106,107]

Predictors of Mortality

In GBS, the mortality rate varies from 3% to 7% overall and is around 20% in patients who become ventilator dependent. Regional variation does, however, exist as evidenced by the high mortality rate of 41% among ventilated patients in low-resource settings which, in addition to being caused by a lack of adequate intensive care facilities or subspecialty care, may also be linked to the absence of immunomodulatory treatments and the presence of the unfavorable risk factor of prior gastroenteritis for a poor prognosis.[108] Despite the fact that GBS is more common in men than in women, sex is not a reliable indicator of prognosis.[109] Data on disparities in GBS outcomes based on sex, race, or ethnicity are lacking.

Advanced age, severe disease, associated comorbidities, pulmonary and cardiac complications, use of mechanical ventilation, and presence of systemic infection are all indicators of a higher chance of death.[110] Acute respiratory distress syndrome, infections, pulmonary emboli, and sudden cardiac arrest are the most prevalent causes of death. These events can happen during the acute and recovery periods, indicating the need for continued supportive care.[111]

Prognosis in Special Situations

While studies have found no appreciable variations in the clinical manifestations of GBS linked with COVID-19,[112] Zika-associated GBS can be associated with

higher rates of bulbar or facial weakness, dyspnea, need for mechanical ventilation, and residual facial and bulbar deficits at 6 months.[113,114]

New Prognostic Markers

A 2020 study determined cutoff levels for serum neurofilament light chain at the time of acute illness that correlated with the probability of being able to walk and run independently 1 year from disease onset. Additionally, neurofilament light chain levels were higher in those with the pure motor variant, Miller Fisher syndrome, and preceding diarrheal illness than in individuals with a respiratory prodrome and sensorimotor GBS.[115]

KEY POINT

- The overall mortality rate of patients with GBS varies from 3% to 7% overall and is around 20% in patients who become ventilator dependent.

TRENDS AND FUTURE STUDIES

Despite the advances in our understanding of GBS, many uncertainties remain, and the only available immunotherapies are IVIg and plasma exchange. Future trends include understanding the role of host genetic factors, new diagnostic tools and biomarkers, vaccine safety studies, cost-effective strategies such as small-volume plasma exchange, development of prognostic models, therapeutic interventions targeting the hyperactive immune system, and promoting regeneration (different strategies are summarized in the literature[2,56]).

CONCLUSION

GBS is an immune-mediated disorder characterized by the presence of inflammation and complement activation, which targets either myelin or axons, resulting in several clinical variants. Despite the availability of immunotherapy, novel diagnostic techniques and disease-specific therapeutic strategies tailored to the needs of each patient are still needed.

USEFUL WEBSITES

INTERNATIONAL GBS OUTCOME STUDY
The International GBS Outcome Study (IGOS) is the largest and longest prospective trial that provided a forum for the collection of extensive data to identify clinical and biological determinants and predictors of disease course in patients with GBS.

gbstools.erasmusmc.nl

GBS/CIDP FOUNDATION INTERNATIONAL
This website offers details on GBS and CIDP, as well as support for patients and their families, news about activism, and volunteer opportunities.

gbs-cidp.org/

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Chronic Immune-Mediated Demyelinating Neuropathies

By Karissa Gable, MD

ABSTRACT

OBJECTIVE: **This article is an overview of chronic demyelinating neuropathies and highlights the phenotypic categorization, diagnosis, and treatment of chronic immune-mediated neuropathies. The clinical and diagnostic characteristics of other chronic demyelinating neuropathies that are common mimics of immune-mediated neuropathies are also discussed.**

LATEST DEVELOPMENTS: **The underlying pathophysiology of chronic demyelinating neuropathies is heterogeneous, and components of both humoral and cellular immune responses are thought to play a role in the immune-mediated types of chronic demyelinating neuropathy. The role of the humoral response is highlighted with a specific focus on the relatively recent discovery of antibody-mediated antinodal and paranodal demyelinating neuropathies. Additionally, new diagnostic criteria for some of the chronic demyelinating neuropathies, as well as ways to differentiate chronic inflammatory demyelinating polyradiculoneuropathy from other chronic demyelinating polyneuropathies, are discussed.**

ESSENTIAL POINTS: **Chronic demyelinating neuropathies can present with overlapping clinical characteristics with seemingly subtle variations. It is clinically important to differentiate these types of neuropathies because the treatment and management can vary and affect prognosis.**

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Address correspondence to Dr Karissa Gable, DUMC 3909, Durham, NC 27710, karissa.gable@duke.edu.

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INTRODUCTION

Chronic demyelinating neuropathies can originate from a broad range of inherited, metabolic, toxic, systemic, and immune-mediated etiologies. Similarities in clinical presentations require careful attention to the evolution of symptoms, clinical examination findings, and supportive data to establish a definitive diagnosis. Accurate diagnosis is important because some types of chronic demyelinating neuropathies, particularly chronic inflammatory neuropathies, can be functionally debilitating if not diagnosed and treated properly. This article is an overview of the defining characteristics of these types of neuropathies as well as a more detailed discussion of the diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and CIDP variants.

KEY POINTS

- Accurate diagnosis of chronic demyelinating neuropathies is important because some types, particularly chronic inflammatory neuropathies, can be functionally debilitating if not diagnosed and treated properly.

- Typical chronic inflammatory demyelinating polyneuropathy (CIDP) accounts for approximately 50% to 60% of all cases and presents with symmetric proximal and distal upper and lower extremity weakness and sensory loss affecting at least two limbs with areflexia that is progressive over a time period greater than 2 months.

- Up to 16% of patients with CIDP can present with acute or subacute CIDP, and clinical monitoring is required to tell if the diagnosis is in fact CIDP.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Although rare, CIDP is a treatable neuropathy with an incidence of 1.6 per 100,000 per year and prevalence of 8.9 per 100,000.[1,2] The symptoms can include motor and sensory symptoms that occur in a progressive or relapsing fashion. The typical clinical presentation involves motor and sensory symptoms that are symmetric, whereas the CIDP variants can present with a heterogeneous constellation of symptoms.

Clinical and Electrophysiologic Features

The clinical phenotype of typical CIDP accounts for approximately 50% to 60% of all cases of CIDP and presents with symmetric proximal and distal upper and lower extremity weakness and sensory loss affecting at least two limbs with areflexia that is progressive over a time period greater than 2 months.[3-5] CIDP can be relapsing with intermittent recurrence of symptoms, monophasic, or progressive.[6] Electrophysiologic features are discussed in detail in the updated CIDP diagnostic and treatment criteria in the 2021 revision of the European Academy of Neurology (EAN) and Peripheral Nerve Society guidelines (TABLE 3-1[5,7-12]). Previously, the 2010 European Federation of Neurological Societies and Peripheral Nerve Society version[13] was utilized most for the diagnosis and management of CIDP because the sensitivity of diagnosis for definite CIDP with those criteria was found to be 73.2% and specificity for the diagnosis was 90.8%. However, limitations arose with accuracy for variants of CIDP.[14] Two 2022 validation studies of the EAN and Peripheral Nerve Society 2021 diagnostic criteria showed that these criteria are roughly equivalent to the European Federation of Neurological Societies and Peripheral Nerve Society criteria and tend to improve the diagnostic accuracy of CIDP variants. The best balance between sensitivity (88% for possible CIDP and 81% for CIDP) and specificity (86% for possible CIDP and 97% for CIDP) was achieved when at least four motor and four sensory nerves were tested on electrodiagnostic studies.[15,16] Generally speaking, a demyelinating pattern is present on electrodiagnostic testing with abnormalities noted in motor and sensory nerves.

Acute-onset and Subacute-onset Chronic Inflammatory Demyelinating Polyradiculoneuropathy

It can be difficult to ascertain the difference between acute-onset CIDP and Guillain-Barré syndrome because the symptoms can appear to be similar. However, Guillain-Barré syndrome is a monophasic acute demyelinating neuropathy and is treated differently.[17] This is discussed in more detail in the article "Guillain-Barré Syndrome" by Ali A. Habib, MD, and Waqar Waheed, MD,[18] in this issue of *Continuum*. Up to 16% of patients can present with acute or subacute CIDP, and monitoring over time is required to tell if the diagnosis is in fact CIDP.[19] If symptoms continue to relapse with greater than three treatment-related fluctuations or continue to progress beyond 8 weeks, then the more likely diagnosis is CIDP.[20] Guillain-Barré syndrome tends to reach a nadir within 4 to 8 weeks. A preceding infection, autonomic dysfunction, respiratory compromise, or bifacial weakness favors Guillain-Barré syndrome as a diagnosis.

European Academy of Neurology and Peripheral Nerve Society Electrodiagnostic Criteria for the Diagnosis of Chronic Inflammatory Demyelinating Polyradiculoneuropathy[a,b,c]

TABLE 3-1

1 Strongly supportive of demyelination

At least one of the following:

a Motor distal latency prolongation ≥50% above the upper limit of normal values (ULN) in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or

b Reduction of motor conduction velocity ≥30% below the lower limit of normal values (LLN) in two nerves, or

c Prolongation of F-wave latency ≥20% above the ULN in two nerves (≥50% if the amplitude of the distal negative peak compound muscle action potential [CMAP] is <80% of LLN), or

d Absence of F waves in two nerves (if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN) and ≥1 other demyelinating parameter[d] in ≥1 other nerve, or

e Motor conduction block: ≥30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥20% of LLN in two nerves; or in one nerve and ≥1 other demyelinating parameter[d] except absence of F-waves in ≥1 other nerve, or

f Abnormal temporal dispersion: ≥30% duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) in ≥2 nerves, or

g Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) prolongation in ≥1 nerve[7] and ≥1 other demyelinating parameter[d] in ≥1 other nerve

2 Weakly supportive of demyelination

As in (1) but in only one nerve

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[a] Reprinted with permission from Van den Bergh PYK, et al, J Peripher Nerv Syst.[5] © 2021 European Academy of Neurology and Peripheral Nerve Society.

[b] These criteria have been established by using a frequency filter bandpass of 2 Hz to 10 kHz for all parameters, except for distal CMAP duration prolongation where separate criteria were defined for four different low-frequency filters of 2 Hz, 5 Hz, 10 Hz, and 20 Hz. Skin temperature should be maintained to at least 33°C (91°F) at the palm and 30°C (86°F) at the external malleolus.

[c] Extensiveness of motor nerve conduction studies (number of nerves to be studied and proximal studies):

- To apply motor nerve conduction criteria, the median, ulnar, (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested.
- If criteria are not fulfilled, the same nerves are tested at the other side, or the ulnar and median nerves are stimulated at the axilla and at the Erb point.
- Motor conduction block or slowing is not considered in the ulnar nerve across the elbow or the peroneal nerve across the knee.
- Between the Erb point and the wrist, at least 50% CMAP amplitude reduction is required for conduction block in the ulnar and median nerves. Proximal studies of the median nerve may require collision techniques to avoid ulnar nerve components in the median nerve CMAP when recorded from the abductor pollicis brevis muscle (but not when recorded from the flexor carpi radialis muscle).[8-12]
- For ulnar motor conduction block in the forearm, a Martin-Gruber anastomosis should be ruled out with stimulation of the median nerve at the elbow recording over the abductor digiti minimi muscle.
- For median motor conduction block in the forearm, costimulation of the ulnar nerve at the wrist must be ruled out. Stimulation of the median nerve at the wrist while simultaneously recording over the abductor pollicis brevis muscle and the abductor digiti minimi muscle can detect ulnar nerve costimulation; stimulation should be adapted so that no CMAP is recorded from the ulnar nerve-innervated abductor digiti minimi muscle.
- If distal CMAP amplitudes are severely reduced (<1 mV), recording from more proximal muscles innervated by the peroneal, median, ulnar, or radial nerve may be attempted to demonstrate motor nerve conduction abnormalities meeting electrodiagnostic criteria.

[d] Any nerve meeting any of the criteria (a through g).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy Variants

CIDP has several clinical phenotypic variants. The variants can have a combination of motor and sensory findings that are asymmetric, purely motor, purely sensory, or distally patterned. Approximately 50% of the CIDP variants phenotypically change over time to a more typical pattern of weakness.[4] TABLE 3-2[5] summarizes the features of these variants.

DISTAL CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. Distal CIDP presents clinically with symptoms of symmetric sensory loss and distal weakness in the upper and lower extremities along with gait abnormality. Approximately two-thirds of patients with this clinical phenotype have an IgM paraprotein. Anti–myelin-associated glycoprotein (MAG) antibodies should also be tested in this clinical phenotype because anti-MAG neuropathy is not considered to be CIDP but has similar clinical features.

MULTIFOCAL CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. Multifocal CIDP, also described as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis-Sumner syndrome, is a variant of CIDP that can present clinically with asymmetric weakness and sensory loss affecting the upper or lower extremities. Clinical examination findings include diminished reflexes, asymmetric weakness, and sensory loss. Isolated upper extremity symptoms have also been reported and could appear to clinically overlap with multifocal motor neuropathy (MMN).[21] The key distinguishing feature in this situation is the clinical combination of motor and sensory

TABLE 3-2 **Chronic Inflammatory Demyelinating Polyradiculoneuropathy Variants[a]**

Variants	Symptoms	Signs	Electrophysiologic findings
Distal	Distal sensory loss and muscle weakness predominately in lower limbs	Sensory loss in the distal upper and lower limbs, weakness lower worse than upper limbs, distally absent or reduced reflexes	Demyelinating features in motor and sensory nerves
Focal	Limb onset	Weakness and sensory changes in one limb	Demyelinating features in the affected limb
Motor	Symmetric distal and proximal symptoms	Motor weakness, normal sensation, reduced or absent reflexes	Generalized motor demyelination; sensory fibers are often spared, but if sensory fibers are involved, motor-predominant involvement still occurs
Sensory	Symmetric distal and proximal sensory symptoms	Diffusely reduced or absent reflexes, normal motor strength	Prolonged somatosensory evoked potential latencies; motor responses generally normal, sensory responses normal or low amplitude; if motor fibers are involved, sensory-predominant involvement still occurs
Multifocal	Asymmetric weakness and sensory changes	Reflexes may be normal in unaffected limbs	Multifocal demyelination in motor and sensory nerves

[a] Data from Van den Bergh PYK, et al, J Peripher Nerv Syst.[5]

symptoms with correlative multifocal demyelinating electrophysiologic changes in motor and sensory nerves. In contrast, MMN, despite typically manifesting with clinical symptoms in the upper extremities, presents with only motor weakness and demyelinating electrophysiologic changes in motor nerve conduction studies with normal sensory responses. This is important to distinguish because the multifocal CIDP variant responds to steroids or intravenous immunoglobulin (IVIg); MMN is typically treated with IVIg only because steroids either do not help symptoms or can make symptoms worse.[22] Additionally, motor-predominant CIDP can worsen with steroid treatment.

FOCAL CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. Focal CIDP, is quite rare and presents with symptoms localizable by electrophysiologic findings or imaging studies to the brachial or lumbosacral plexus or single nerve of one limb and clinically manifesting with motor weakness and sensory changes.[23] Typically, electrophysiologic motor and sensory nerve involvement is present but restricted to the clinically affected limb.

MOTOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. The motor CIDP variant presents clinically with only motor weakness and no sensory symptoms in a proximal and distal pattern with reduced muscle stretch reflexes. Of note, this differs from MMN, which is a condition that phenotypically presents with asymmetric, distal, and upper limb–predominant pure motor weakness without sensory involvement. Electrophysiology demonstrates generalized motor nerve demyelinating changes, sparing sensory studies. If the sensory nerve conduction studies are abnormal in clinically motor CIDP, the diagnosis is motor-predominant CIDP.

SENSORY CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. This is also a rare variant of CIDP with 5% to 15% of patients presenting with pure sensory symptoms in a proximal and distal pattern with absent or reduced reflexes throughout. Electrophysiologic changes reflect normal or low-amplitude sensory responses with normal motor nerve conduction studies. If the motor nerve conduction studies demonstrate conduction block or conduction velocity slowing without clinical motor weakness, the diagnosis is sensory-predominant CIDP. Patients suspected of having clinically sensory CIDP with normal motor and sensory nerve conduction studies may have chronic immune sensory polyradiculopathy (CISP). Somatosensory evoked potentials are often found to be abnormal due to the involvement of the sensory roots proximal to the dorsal root ganglia. Although this condition is thought to be autoimmune in nature, it was considered not to be a CIDP variant in the guidelines.[5,24]

Pathogenesis

The underlying pathophysiology of CIDP, both typical CIDP and the CIDP variants, involves the humoral and cellular immune-mediated systems. T-cell dysregulation with impaired suppressive capacity of T regulatory cells, as well as upregulation of inflammatory T cells and cytokines and increased macrophage activation, has been demonstrated in CIDP.[25,26] Antibody-mediated disease is less understood, although the recent discovery[27,28] of the antineurofascin- and anticontactin-mediated paranodal and nodal demyelinating neuropathies

KEY POINTS

- CIDP variants can have a combination of motor and sensory findings that are asymmetric, purely motor, purely sensory, focal, or distally patterned.
- Multifocal CIDP is a variant of CIDP that can present clinically with asymmetric weakness and sensory loss affecting the upper or lower extremities.
- The underlying pathophysiology of CIDP, both typical CIDP and the CIDP variants, involves the humoral and cellular immune-mediated systems.

supports a humoral immune-mediated process, as well. Complement-dependent mechanisms of action have also been reported.[27,28]

Supportive Clinical and Diagnostic Testing

Several tests can be used to support the diagnosis of CIDP when the diagnosis is possible but not definitive. Response to treatment, spinal fluid testing, antibody testing, imaging with MRI or ultrasonography, and rarely nerve biopsy are supportive investigations that can be performed to confirm the diagnosis. None of the supportive testing results, however, should be used in isolation in making the diagnosis of CIDP.[29]

RESPONSE TO TREATMENT AS DIAGNOSTIC CONFIRMATION. The EAN and Peripheral Nerve Society guidelines recommend that an objective response to treatment with one of the first-line therapies is considered supportive of the clinical diagnosis of CIDP.[5] A lack of initial response does not completely exclude the diagnosis either; however, improvement is expected to take place within the first 3 to 6 months of treatment. Approximately 80% to 90% of patients show improvement with one of the first-line treatments.[30-33] If improvement with one of the first-line therapies is not seen, reconsidering the diagnosis or adjusting treatment is recommended. Treatment options are discussed later in this article.

Objective measures that can be used to assess the level of disability include the Inflammatory Rasch-built Overall Disability Scale (I-RODS) and the Inflammatory Neuropathy Cause and Treatment (INCAT) scale.[34,35] The Medical Research Council sum score, modified INCAT Sensory Sum Score, Neuropathy Impairment Score, or grip strength dynamometry can be used to assess impairment.[36-38] TABLE 3-3 provides a general guide for changes in outcome measure scores that correlate with meaningful improvement used in clinical trials. Higher values increase the specificity, and averaging values over at least 3 days can help improve specificity as well.[38] It is recommended that improvement be noted on at least one measure of disability in addition to one measure of impairment following treatment to demonstrate adequate support of the diagnosis.[5]

TABLE 3-3

Scales to Measure Outcomes

Outcome Measures	Guide for meaningful changes (no strict cutoffs)
Inflammatory Rasch-built Overall Disability Scale (I-RODS)	Greater than equal to a 4-centile metric score change
Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale	Greater than or equal to 1 point
Modified INCAT Sum Score	Greater than or equal to 2 points
Medical Research Council Sum score (0-60)	Greater than or equal to 2-4 points
Grip strength	
Vigorimeter	Greater than or equal to 8-14 kilopascals (kPa)
Hand grip dynamometer	Greater than or equal to 10%

IMAGING. Both MRI and ultrasonography can be used as imaging modalities to support the diagnosis of CIDP. Typically, MRI of the cervical or lumbar spine is performed with and without contrast to determine if enlargement, hyperintensity, or enhancement of the nerve roots is present. MRI of the brachial plexus or lumbosacral plexus can also be performed, and the supportive imaging findings include focal nerve enlargement, hyperintensity, or enhancement. Importantly, CIDP is not the only disease process that can demonstrate these findings. Other diseases that may overlap radiographically include hereditary amyloidosis, Charcot-Marie-Tooth disease, paraprotein-related neuropathies, neurofibromatosis, diabetic radiculoplexus neuropathies, leprosy, MMN, and neurolymphomatosis.[5]

Ultrasound imaging can be used to assist with confirming the diagnosis. The specific criteria note that nerve enlargement of the cross-sectional area should be seen in at least two sites in the proximal median nerve segments or brachial plexus. A cross-sectional area of the median nerve must be greater than 10 mm^2 at the forearm, greater than 13 mm^2 in the upper arm, greater than 9 mm^2 at the trunk level, or greater than 12 mm^2 at the nerve roots. Of course, ultrasonography is prone to the same mimics as MRI, and these diagnoses should be excluded in the appropriate setting.[5]

SPINAL FLUID. CSF testing can help support the diagnosis of CIDP. Typically, in CIDP albuminocytologic dissociation is seen with a normal nucleated cell count and elevated protein levels. A CSF pleocytosis greater than 10 cells/mm^3 and particularly greater than 50 cells/mm^3, should raise suspicion for an alternative etiology such as an infectious or potentially malignant etiology.[5,39] Other factors aside from inflammatory neuropathy can increase spinal fluid protein, including diabetes or spinal stenosis. Generally, if CSF protein levels are between 45 mg/dL and 60 mg/dL, especially when the patient is older than 50 years, use caution interpreting this finding in the context of the individual patient. Additionally, avoid using CSF protein level measurement as the sole supportive test for the diagnosis of CIDP. In practice, CSF protein greater than 100 mg/dL provides strong evidence in support of the diagnosis of CIDP. There is, however, insufficient evidence to provide exact cutoff values.[40,41]

NERVE BIOPSY. Because of associated morbidity and poor sensitivity and specificity, nerve biopsy is not performed with regularity in patients who may have CIDP. Instead, the diagnosis should first be pursued with clinical, electrodiagnostic, laboratory, or imaging studies. Findings from a nerve biopsy that would support the diagnosis of CIDP include thinly myelinated axons and onion bulb formation, demyelinating features on teased fiber preparations and electron microscopy, or perivascular macrophage infiltration. Nerve biopsies should be performed only at centers with experienced surgeons and pathologists.[5]

DIFFERENTIAL DIAGNOSIS OF CHRONIC IMMUNE-MEDIATED DEMYELINATING NEUROPATHIES

When considering CIDP, it is important to consider other diagnostic possibilities. In one study, approximately one-half of patients diagnosed with CIDP were ultimately found to have an alternative diagnosis.[29] Diseases that have been misdiagnosed as CIDP include inherited neuropathies such as Charcot-Marie-Tooth disease, hereditary amyloidosis, MMN, motor neuron disease, idiopathic

KEY POINTS

- Response to treatment, spinal fluid testing, antibody testing, imaging with MRI or ultrasonography, and rarely nerve biopsy are supportive investigations that can be performed to confirm the diagnosis of CIDP.
- It is recommended that improvements be noted objectively on at least one measure of disability and on one impairment scale following treatment to demonstrate adequate support of the diagnosis of CIDP, particularly in cases of possible CIDP.
- Both MRI and ultrasonography can be used as imaging modalities to support the diagnosis of CIDP.
- MRI evidence of focal nerve enlargement, hyperintensity, or enhancement are not specific to CIDP and can also be seen in hereditary neuropathy and malignancy.
- CIDP is characterized by albuminocytologic dissociation or a normal CSF nucleated cell count and elevated protein levels.
- Up to one-half of patients initially diagnosed with CIDP may be ultimately found to have an alternative diagnosis.

axonal neuropathy, and small fiber neuropathy among other diagnoses. This section includes a detailed discussion of the more common mimics, including anti-MAG neuropathy, antiparanodal and antinodal chronic immune-mediated demyelinating neuropathy, MMN, CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin IgM paraprotein, cold agglutinins and disialosyl antibodies), POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome, and hereditary demyelinating neuropathies, as well as an overview of all mimics of chronic demyelinating neuropathies in TABLE 3-4.[42]

Anti–Myelin-associated Glycoprotein Neuropathy

Paraprotein-related chronic demyelinating neuropathies are discussed in detail in the article “Paraproteinemic Neuropathies” by Said R. Beydoun, MD, FAAN, and Leila Darki, MD,[43] in this issue of *Continuum*. Briefly, patients with anti-MAG neuropathy often present with a chronic distal lower extremity sensorimotor polyneuropathy. Gait abnormalities with sensory ataxia and tremor are also present. This condition presents more often in men than women. Greater than 50% of patients who present with a distal demyelinating neuropathy associated with IgM monoclonal gammopathy develop antibodies against MAG. Electrophysiologically, evidence of primarily distal slowing with pronounced distal latency prolongation and secondary axon loss can be seen.[44]

Antiparanodal and Antinodal Chronic Immune-mediated Demyelinating Neuropathy

The recent discovery of a population of patients with antibody-mediated demyelinating neuropathy with a CIDP-like phenotype is of particular interest because it differentiates a group of patients who respond differently to treatment. Approximately 10% of patients meeting the electrodiagnostic criteria for CIDP have antibodies against the node of Ranvier nodal and paranodal proteins. Specifically, antibodies target the nodal neurofascin 186 (NF186) or paranodal proteins contactin-1 (CNTN1), contactin-associated protein 1 (CASPR1), or neurofascin 155 (NF155). The majority of these antibodies reflect an immunoglobulin G4 (IgG4)–mediated response and respond only partially or not at all to typical first-line treatments for CIDP. FIGURE 3-1[45] shows an illustrative overview of the area of the nerve affected in these types of neuropathies. Additional clinical features that manifest in these types of neuropathies can be clinically differentiating. Paranodal and nodal antibody–positive patients are more likely to be adults, to be male, and to present with a severe and symmetric, distal, motor-predominant rapidly progressive disease. Tremor and sensory ataxia more notably manifest in this patient population as compared with patients with typical CIDP. Nephrotic syndrome has been reported to occur more commonly in patients with CNTN1 antibodies. Panneurofascin antibody positivity has been associated with underlying lymphoma, myeloma, and leukemia.[46] CASE 3-1 illustrates a characteristic presentation of this type of neuropathy.

Multifocal Motor Neuropathy

MMN, although not technically a variant of CIDP, is an immune-mediated chronic demyelinating neuropathy and therefore is discussed here.

Clinically, the presentation of MMN is asymmetric, distal upper limb predominant with pure motor symptoms. Often the finger flexors are relatively spared, and foot drop may be the first symptom in one-third of patients. There is a male predominance and a mean age of onset around 40 years of age. Fasciculations and cramps are reported in about 40% of patients.[47,48]

The diagnosis of MMN requires motor nerve involvement in at least two nerves for more than 1 month. Anti-GM1 antibodies are seen in some but not all patients with MMN, and the absence of GM1 antibodies does not exclude the diagnosis. In patients with MMN, the presence of anti-GM1 antibodies ranges from 30% to 80%.[13] Clinically, no sensory symptoms are present. Reflexes are often absent or diminished in the affected limb. Electrophysiology often demonstrates demyelinating features with conduction block in the motor nerves. However, if the conduction block is very proximal or distal, it may be more difficult to detect. If any signs of sensory loss, upper motor neuron dysfunction, bulbar involvement, or symmetric weakness are present, one should consider an alternative diagnosis. CASE 3-2 shows how MMN and multifocal CIDP can clinically appear similar and that supportive diagnostic testing is helpful in those cases.

CANOMAD

CANOMAD is a rare chronic demyelinating neuropathy that presents with symptoms of ocular and bulbar weakness, as well as a sensory ataxia and paresthesias or hypoesthesia. It results in moderate disability. Patients have a serum monoclonal IgM gammopathy. Electrophysiologic studies demonstrate a demyelinating or axonal pattern.[49]

POEMS Syndrome

Clinical symptoms of POEMS syndrome can mimic typical CIDP, sometimes with more distal weakness. Pain is a more frequent feature of POEMS syndrome–related neuropathy compared with CIDP. Electrophysiologic findings are often uniformly demyelinating, lack conduction block, and typically show axon loss.[50]

The diagnosis of POEMS syndrome relies on the presence of a polyneuropathy that is typically demyelinating and a monoclonal immunoglobin protein that is almost always of the lambda variety. These are the mandatory major criteria. Other criteria are summarized in TABLE 3-5.[51] POEMS syndrome may not present with all of the characteristics that define the syndrome. Elevated vascular endothelial growth factor (VEGF) is considered one of the other major criteria required to make the diagnosis. It is important to note that the VEGF level can be affected by prednisone and other immunosuppressive treatments, lowering it artificially and thus making the diagnosis of POEMS syndrome challenging.[50] This diagnosis should be suspected in patients who have no response to the typical CIDP treatments. For more information about POEMS syndrome, refer to the article "Paraproteinemic Neuropathies" by Said R. Beydoun, MD, FAAN, and Leila Darki, MD,[43] in this issue of *Continuum*.

Hereditary Demyelinating Neuropathies

Demyelinating hereditary neuropathies can mimic immune-mediated demyelinating neuropathies and are discussed extensively in the article "Hereditary Neuropathies" by Reza Sadjadi, MD, and Leslie Hayes, MD,[52] in this issue of *Continuum*. TABLE 3-6 includes a summary of when alternative diagnoses to CIDP should be considered.

KEY POINTS

- Greater than 50% of patients who present with a distal demyelinating neuropathy associated with IgM monoclonal gammopathy develop antibodies against myelin-associated glycoprotein.
- Approximately 10% of patients meeting the electrodiagnostic criteria for CIDP have antibodies against node of Ranvier nodal and paranodal proteins.
- Anti-GM1 antibodies are seen in some but not all patients with multifocal motor neuropathy, and the absence of GM1 antibodies does not exclude the diagnosis.
- Pain is often a more prominent feature of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome–related neuropathy compared with CIDP.

TABLE 3-4 Differential Diagnosis of Chronic Demyelinating Polyneuropathies[a]

Disease	Key clinical features	Key electrophysiologic features	CSF protein	Treatment
Immune				
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Peak symptom evolution at 4 weeks without progression beyond 8 weeks	Early F-wave and H-reflex prolongation, demyelinating features peak at 2-4 weeks	Normal or elevated	IVIg, plasma exchange
Myelin-associated glycoprotein (MAG)	Slow clinical progression with distal phenotype	Distal predominant slowing	Elevated	Supportive, IVIg or rituximab
Multifocal motor neuropathy (MMN)	Multifocal weakness with no upper motor neuron signs or sensory loss	Motor nerve conduction block and other acquired demyelinating motor features	Normal or elevated	IVIg
POEMS syndrome	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes	Uniform conduction velocity (CV) slowing, reduced motor and sensory amplitudes	Elevated	Treatment of underlying plasma cell disorder (chemotherapy, radiotherapy, stem cell transplantation)
Drug-induced	Associated with tumor necrosis factor α (TNF-α) antagonists, interferon alfa therapy, tacrolimus, bortezomib, pembrolizumab	Appears similar to chronic inflammatory demyelinating polyneuropathy (CIDP)	Normal or elevated	Drug withdrawal, corticosteroid, IVIg
Metabolic				
Diabetic	Length-dependent large and small fiber most common; plexopathy or focal neuropathy also occur	Axonal; mild to moderate CV slowing without conduction block (CB) or temporal dispersion (TD) may be seen	Normal or elevated	Optimize blood sugar control, supportive
Uremic	Glomerular filtration rate often < 12 mL/min	Axonal; mild to moderate CV slowing without CB or TD may be seen	Normal or elevated	Optimize renal function, supportive
Toxic				
Amiodarone	Subacute to chronic progression, symmetric sensorimotor, often distal, may affect proximal muscles	Axonal; mild CV slowing and distal latency (DL) prolongation may be seen	Normal	Stop exposure, supportive care
Ethylene glycol	Renal and cardiac toxicity, cranial nerve changes, central nervous system depression	Axonal	Elevated	Stop exposure, supportive care
Diphtheria	Bulbar and respiratory weakness common, evolves over 2-3 weeks	Similar to CIDP	Elevated	Antibiotics, antitoxin

CONTINUED ON PAGE 1367

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Disease	Key clinical features	Key electrophysiologic features	CSF protein	Treatment
Systemic				
Sarcoid	Pulmonary, skin, ocular, muscle, endocrine, cranial nerve or central nervous system involvement	Axonal; may be multifocal or length dependent	Normal or elevated	Corticosteroid, immunosuppressive therapy, TNF-α inhibitor
Inherited				
Amyloid	Pain and dysautonomia often with cardiac or gastrointestinal involvement; *TTR* gene variation	Axonal; mild to moderate CV slowing mimicking CIDP may be seen	Normal or elevated	Stabilizers, mRNA silencers
Hereditary neuropathy with lability to pressure palsies (HNPP)	Multifocal neuropathy after mild trauma or compression	Mild CV slowing and CB at compressible sites, prolonged DL	Normal	Supportive care
Charcot-Marie-Tooth disease type 1 (CMT1)	Onset at variable ages, motor symptoms predominate, sensory symptoms present	Uniform CV slowing typically without CB or TD	Normal or mildly elevated	Supportive care
Fabry disease	X-linked, associated with strokes, angiokeratomas, premature atherosclerosis	Slow CV, prolonged DL, may be normal early on in disease	Normal or elevated	Enzyme replacement
Refsum disease	Autosomal recessive, early-onset retinitis pigmentosa, cerebellar ataxia, hearing loss, cardiac conduction disease	Demyelinating with severe CV slowing	Elevated	Limit intake of phytanic acid
Metachromatic leukodystrophy (MLD)	Autosomal recessive arylsulfatase A gene variation, often presents early	CV slowing without CB	Elevated	Supportive; stem cell transplantation (SCT) research ongoing
Krabbe disease	Autosomal recessive, galactosylceramide beta-galactosidase gene variation, variable age of onset	Slow CV occasionally with CB	Elevated	Supportive; SCT research ongoing
Mitochondrial				
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Childhood onset, myopathy, ophthalmoplegia, neuropathy, gastrointestinal symptoms, encephalopathy	Demyelinating with CV slowing, CB, and TD in some patients	Elevated	Supportive; SCT research ongoing

CSF = cerebrospinal fluid; IVIg = intravenous immunoglobulin; mRNA = messenger ribonucleic acid.
[a] Modified with permission from Allen JA,[42] Continuum (Minneap Minn). © 2017 American Academy of Neurology.

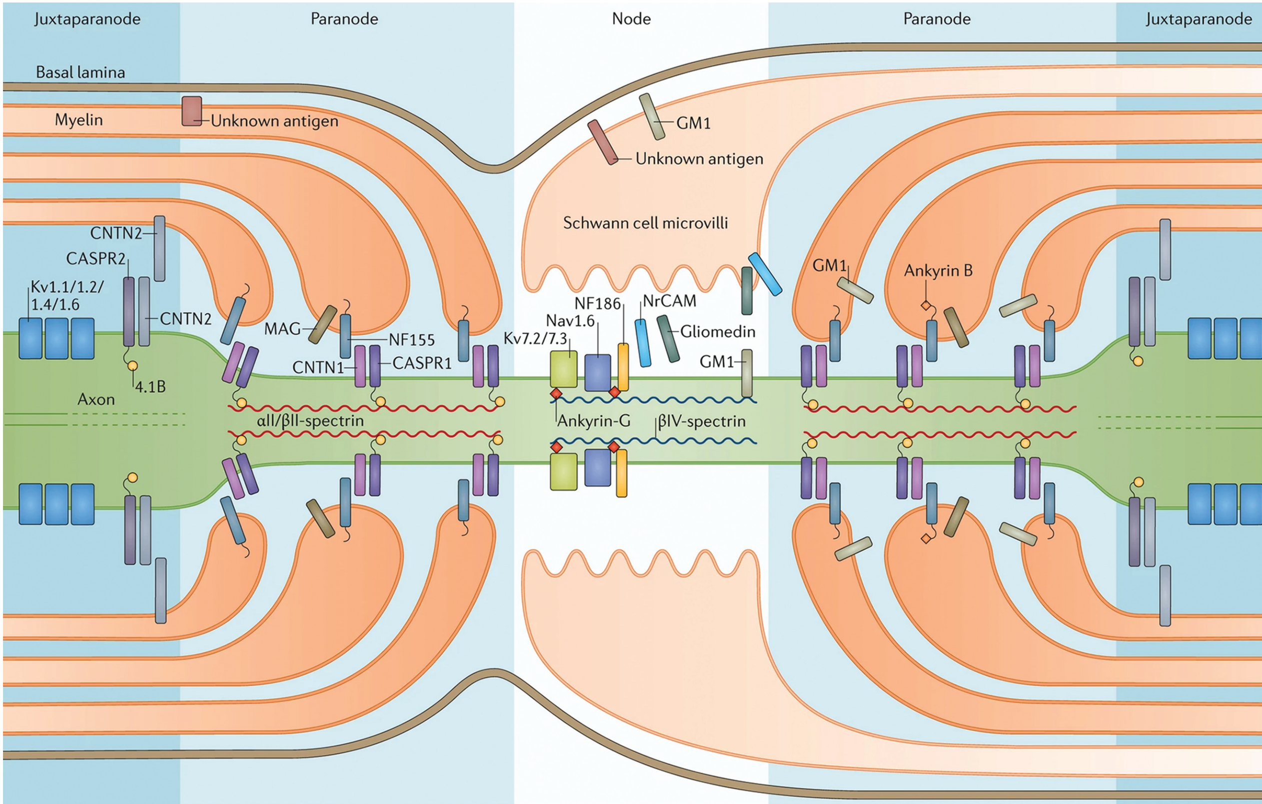

FIGURE 3-1

The node of Ranvier. The illustration shows the structure and key molecular components of the node of Ranvier, including those targeted by autoantibodies in autoimmune neuropathies. Adhesion molecules (NF186, NF155, NrCAM, CNTN1, CNTN2, CASPR1, CASPR2, and MAG) mediate axoglial attachment. Ion channels (Kv7.2/7.3, Kv1.1/1.2/1.4/1.6, and Nav1.6) mediate action potential propagation. Adhesion molecules and ion channels are all linked to the cytoskeleton by proteins, including ankyrins and spectrins. Gliomedin is an extracellular matrix constituent that stabilizes the structure of the nodal area.

CASPR = contactin-associated protein; CNTN = contactin; Kv = voltage-gated potassium channel; MAG = myelin-associated glycoprotein; Nav = voltage-gated sodium channel; NF = neurofascin; NrCAM = neuronal cell adhesion molecule.

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TREATMENT OF CHRONIC IMMUNE-MEDIATED DEMYELINATING NEUROPATHIES

Recommendations for the treatment of immune-mediated chronic demyelinating neuropathies can vary and involve the use of immunomodulatory or immune-suppressive treatments. This section provides an overview of an approach to treatment and the types of treatment for the most common immune-mediated chronic demyelinating neuropathies.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Variants

Treatment of typical CIDP and its variants is similar and includes IVIg, steroids, or plasma exchange as first-line induction and maintenance therapies.[5] Subcutaneous immunoglobulin is considered a first-line maintenance treatment. Selection and optimization of treatment depend on several factors, including consideration of patient comorbidities, cost, accessibility, and risks versus benefits of each treatment. It is recommended to set expectations for prognosis and degree

of improvement that will be seen with treatment and introduce the concept of objective measures of improvement before or at the initiation of treatment. It is also helpful for patients to understand the concept of a wearing-off effect of treatment before the next dose is given and to monitor for those symptoms, which typically involve some degree of worsening of functional impairment or disability.

IV AND SUBCUTANEOUS IMMUNOGLOBULIN. Induction dosing typically follows a regimen of 2 g/kg, divided over 4 to 5 days. This is followed by two to five repeated doses of 1 g/kg IVIg every 3 to 4 weeks to determine effectiveness. Maintenance dosing is often 1 g/kg every 3 to 4 weeks, with extension of the interval or a reduction of the dose when a plateau of improvement is achieved and the patient is clinically stable.[42] Tapering of medication should be attempted approximately every 6 to 12 months once clinical stability has been achieved in the first 2 to 3 years of treatment. From that point, tapering treatment can then be attempted every 1 to 2 years. Subcutaneous immunoglobulin is recommended primarily for maintenance dosing. The decision to transition from IVIg to subcutaneous immunoglobulin can depend on several factors including patient preference, venous access limitations, or side effect profile. Transition from IVIg to subcutaneous immunoglobulin can occur in a 1:1 dosing transition. For example, a patient on 80 g IVIg every 4 weeks can transition to 20 g subcutaneous immunoglobulin weekly for an approximately equivalent dose. That dose may need to be adjusted higher to achieve appropriate outcomes. Some of the potential adverse effects of IVIg and subcutaneous immunoglobulin include aseptic meningitis, increased risk of pulmonary embolism or deep vein thrombosis, and headache.[5,35] CASE 3-3 illustrates a switch to an alternative first-line treatment option when a patient has an adverse effect.

CORTICOSTEROIDS. Steroid treatment is considered a first-line option in the treatment of CIDP and CIDP variants. Depending on the severity of the disease and the comorbidities of the patient, one approach would be to start 20 mg to 60 mg daily of oral prednisone and taper after a plateau of improvement has been achieved. Another approach could be to use high-dose methylprednisolone 1000 mg IV daily for 3 to 5 days with IV or oral administration thereafter. No clear recommendation has been determined for the ideal regimen when choosing between initiating the specific regimens of oral prednisone, IV methylprednisolone or dexamethasone. Refer to the EAN and Peripheral Nerve Society guidelines for further guidance with respect to algorithms for induction and maintenance treatment.[5]

PLASMA EXCHANGE. Although plasma exchange is considered a first-line treatment, it has some practical limitations. This type of treatment works best for patients with good venous access, ideally with the use of peripheral venous access. Initial treatment begins with five exchanges every other day over the course of 2 weeks, which typically requires hospitalization. Depending on the frequency of exchanges needed, tunneled catheters may be needed, and because of venous access difficulties, long-term use of plasma exchange for maintenance therapy is challenging.

OTHER TREATMENT OPTIONS FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND ITS VARIANTS. If individual therapies or

CASE 3-1

A 25-year-old man presented with gradually progressive painless weakness for 5 months along with the development of hand tremor and ataxia. Examination demonstrated proximal and distal weakness of the upper and lower extremities, absent reflexes, and loss of sensation in his distal upper and lower extremities. He had an action tremor with low frequency, high amplitude, and marked postural and intention components in both upper extremities and a steppage and wide-based gait. Electrodiagnostic testing demonstrated demyelinating changes in motor nerves with multiple sites of conduction block at sites not associated with nerve compression. Sensory and motor nerve conduction studies were consistent with the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The patient was started on a loading dose of 2 g/kg intravenous immunoglobulin (IVIg), given over a period of 5 days, and subsequent doses every 3 weeks of 1 g/kg, given over a period of 1 to 3 days. He showed mild improvement.

Corticosteroids were started at 40 mg daily with some additional improvement, but after several months of therapy and changing the interval of IVIg from every 3 weeks to every 2 weeks, the patient still had only a partial response to therapy. Because of concern about the diagnosis given the lack of a complete response after 6 months of treatment, spinal fluid was obtained and demonstrated albuminocytologic dissociation with a very elevated CSF protein of 435 mg/dL. Antineurofascin and anticontactin antibody testing revealed antineurofascin 155 (NF155) antibodies. Rituximab was given as two 1000-mg IV infusions separated by 2 weeks. After 3 months, he demonstrated significant improvement. IVIg and steroids were slowly tapered off. Outcome measures with grip strength, timed up-and-go testing, and Inflammatory Rasch-built Overall Disability Scale (I-RODS) and Inflammatory Neuropathy Cause and Treatment (INCAT) scores were improved as well.

COMMENT

This case highlights the clinical phenotype of patients with antineurofascin-mediated demyelinating neuropathy. Typically, patients are younger at onset, are noted to have a tremor and ataxia more than in typical CIDP cases, and have only a partial or no response to the first-line treatments of steroids or IVIg or both. CSF protein is often elevated. Rituximab can be an effective treatment for these patients. Outcome measures may be useful in providing supportive information for treatment response.

CASE 3-2

A 52-year-old man developed gradually progressive painless bilateral grip weakness over 4 months. Examination demonstrated weakness of the abductor pollicis brevis, flexor pollicis longus, interossei, and shoulder abductors bilaterally. He also had reduced sensation in his fingertips bilaterally and absent reflexes in his upper and lower extremities, although his lower extremities had normal strength. Electrodiagnostic testing demonstrated prolonged motor distal latencies, slowed conduction velocities, and conduction block in both median nerves, as well as demyelinating changes in both ulnar nerves and slowed conduction velocities in the fibular and tibial motor nerves that met the criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Sensory nerve action potentials were absent in both upper extremities. CSF studies demonstrated albuminocytologic dissociation with no nucleated cells and a protein level of 110 mg/dL. MRI of the cervical spine was unremarkable. Anti-GM1 antibodies were negative. He started treatment with a loading dose of 2 g/kg intravenous immunoglobulin (IVIg), given over a period of 4 to 5 days, and subsequent doses every 4 weeks of 1 g/kg, given over a period of 1 to 3 days. Comparison of baseline grip strength dynamometry and the Inflammatory Rasch-built Overall Disability Scale (I-RODS) and Inflammatory Neuropathy Cause and Treatment (INCAT) scores to measures after treatment after two cycles of maintenance treatment demonstrated improvement, as well as improvement on a strength-testing examination. He continued IVIg 1 g/kg with successful tapering to a 6-week dosing interval.

COMMENT

This case highlights the overlap between the clinical presentation of multifocal motor neuropathy (MMN) and the multifocal variant of CIDP. The important features to note are that multiple motor and sensory nerves are involved, and on electrodiagnostic testing, both sensory and motor nerves are affected with demyelinating changes that meet the criteria for diagnosis of CIDP. GM1 antibodies can be, but are not always, present in MMN. Additional supportive diagnostic testing is helpful in complex cases. This is important because treatment can have ramifications as MMN does not respond to steroid treatment and the multifocal variant of CIDP typically does. Finally, using outcome measures such as grip strength in this case in addition to clinical examination every 3 months can help guide treatment decisions for reducing the dose or increasing the interval of treatment.

combination therapy with immunoglobulin and steroids is not effective, steroid-sparing agents can also be considered. Azathioprine, mycophenolate mofetil, or cyclosporine can be used as a maintenance treatment, although no strong evidence has shown that these medications are effective in reducing the need for steroid or immunoglobulin dosing. For patients with a clear diagnosis of CIDP who have no response to first-line treatment, cyclophosphamide or rituximab can be used as well.[5]

Antiparanodal and Antinodal Chronic Immune-mediated Demyelinating Neuropathy

Patients with this type of paranodal or nodal antibody-mediated neuropathy may have only a partial or no response to IVIg, plasma exchange, or steroid treatment. Case series support rituximab as a treatment of choice for patients with antiparanodal and antinodal antibody immune-mediated neuropathy.[5] The response to treatment can occur in weeks to months after starting rituximab and

TABLE 3-5 **POEMS Syndrome Diagnostic Criteria**[a,b]

Mandatory major criteria
Polyneuropathy (typically demyelinating)
Monoclonal plasma cell-proliferative disorder (almost always lambda)
Other major criteria (one required)
Castleman disease[c]
Sclerotic bone lesions
Vascular endothelial growth factor elevation
Minor criteria (one required)
Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
Extravascular volume overload (edema, pleural effusion, or ascites)
Endocrinopathy (adrenal, thyroid,[d] pituitary, gonadal, parathyroid, pancreatic[d])
Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
Papilledema
Thrombocytosis or polycythemia[e]
Other symptoms and signs
Clubbing, weight loss, hyperhidrosis, pulmonary hypertension or restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes.
[a] Reprinted with permission from Dispenzieri A, Am J Hematol.[51] © 2019 Wiley Periodicals, Inc.
[b] The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present.
[c] A Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal plasma cell disorder is not accounted for in this table. This entity should be considered separately.
[d] Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.
[e] Approximately 50% of patients will have bone marrow changes that distinguish it from a typical monoclonal gammopathy of undetermined significance or myeloma bone marrow.[46] Anemia and thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present.

can be sustained for up to 1 to 2 years.[53] Options for dosing include the standard two 1000-mg rituximab IV infusions separated by 2 weeks with redosing with recurrence of symptoms. Alternatively, one study demonstrated efficacy with 100-mg dosing weekly for 4 weeks and 100-mg dosing per month for 2 months to limit infection risk.[54]

Red Flags for Diagnoses Other Than Chronic Inflammatory Demyelinating Polyradiculoneuropathy[a]

TABLE 3-6

	Typical CIDP	Distal CIDP	Multifocal and focal CIDP	Motor CIDP	Sensory CIDP
Clinical	Subacute, low-frequency tremor, marked ataxia, distal predominance: autoimmune nodopathy phenotype	Family history: Charcot-Marie-Tooth disease or amyloid transthyretin variant (ATTRv) Autonomic features, pain: ATTRv neuropathy, diabetic neuropathy Subacute, low-frequency tremor, marked ataxia, distal predominance: autoimmune nodopathy phenotype	Pain: diabetic radiculoplexopathy, neuralgic amyotrophy Normal sensation: multifocal motor neuropathy Focal: only 1 nerve in 1 limb: nerve entrapment or tumor Family history: hereditary neuropathy with liability to pressure palsies	Dyspnea, dysarthria, dysphagia: motor neuron disease, myasthenia gravis Family history: hereditary motor neuropathies (familial amyotrophic lateral sclerosis, distal hereditary motor neuropathies, spinal muscular atrophy) Prominent asymmetry at onset: multifocal motor neuropathy	Idiopathic sensory axonal neuropathy Family history: hereditary sensory neuropathy
Laboratory	Fasting blood glucose or hemoglobin A_{1C} (HbA_{1C}) elevated: diabetic neuropathy IgA or IgG monoclonal gammopathy: multiple myeloma, light chain (AL) amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome	Fasting blood glucose or HbA_{1C} elevated: diabetic neuropathy IgA or IgG monoclonal gammopathy: multiple myeloma, AL amyloidosis, POEMS syndrome IgM monoclonal gammopathy: anti–myelin-associated glycoprotein (MAG) neuropathy	Antinuclear antibody/antineutrophil cytoplasm antibody positive: vasculitic neuropathy	Elevated serum creatine kinase level: inflammatory myopathy	Fasting blood glucose or HbA_{1C} elevated: diabetic neuropathy Low vitamin B_{12} level, chemotherapy: sensory neuronopathy IgM monoclonal gammopathy: anti-MAG neuropathy Normal motor and sensory conduction studies: chronic immune sensory polyradiculopathy (CISP)

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M.
[a] Modified with permission from Van den Bergh PYK, J Peripher Nerv Syst.[5] © 2021 European Academy of Neurology and Peripheral Nerve Society.

Anti–Myelin-associated Glycoprotein Neuropathy

Evidence of treatment effectiveness has been limited in randomized controlled trials for this disorder, although trial design may have had some limitations. In patients with mild symptoms and without significant disability, symptomatic treatment for tremor or paresthesia can be provided. If the patient has severe disability or a rapid decline, a course of IVIg, plasma exchange, or other cytotoxic or biologic agents such as rituximab could be offered with consideration of the risks and benefits.[44] Cumulative data demonstrate that rituximab helps improve symptoms in 30% to 50% of patients.[55,56] It is unknown why this treatment has limited efficacy. Of note, patients who have distal CIDP without monoclonal proteins and without anti-MAG antibodies tend to have a response to typical first-line treatments for CIDP.[57]

CASE 3-3

A 56-year-old man presented with gradually progressive painless proximal and distal weakness over the course of 3 months associated with sensory loss in the distal upper and lower extremities. Examination demonstrated mild weakness in his proximal and distal upper and lower extremities, absent reflexes, decreased pinprick to his knees and wrists bilaterally, and a wide-based gait. Electrodiagnostic testing demonstrated conduction block in multiple motor nerves sites not typically prone to compression with significantly slowed conduction velocities, as well as a significant reduction in conduction velocities in the sural and ulnar nerve sensory nerves, meeting the European Academy of Neurology (EAN) and Peripheral Nerve Society electrodiagnostic criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[5] Given the definitive clinical and electrodiagnostic testing, no other testing was performed to confirm the diagnosis. He was started on a loading dose of 2 g/kg intravenous immunoglobulin (IVIg), given over a period of 5 days to assure tolerability. A week after treatment, he had dyspnea on exertion, sought evaluation, and was found to have a pulmonary embolism. He was then switched to pulse-dose IV methylprednisolone as he was averse to daily high-dose oral steroids.

COMMENT

This case highlights the recommendations in the EAN and PNS criteria that, if the clinical and electrodiagnostic testing are confirmatory of a diagnosis of CIDP, then it is not necessary to pursue other supportive testing to confirm the diagnosis. It also illustrates that, in the case of an adverse reaction to one of the first-line treatments, an alternative first-line treatment can be started. In this case, the patient was concerned about the risk of high-dose daily prednisone use and opted to use IV methylprednisolone monthly after an induction dose of 1000 mg daily for 3 days followed by 1000 mg monthly of methylprednisolone. This case also highlights the importance of considering patient preference for the route of treatment when deciding on a therapy because it influences treatment adherence and the ultimate success of treatment.

Multifocal Motor Neuropathy

Several randomized controlled trials support the use of IVIg as a first-line treatment for MMN. Most patients require continued maintenance treatment and can be transitioned to subcutaneous immunoglobulin if needed or preferred. The dosing and interval of treatment should be monitored to prevent axonal loss, which can potentially lead to irreversible cumulative disability. Cyclophosphamide can also be used with consideration of the serious risks associated with this treatment and with limited trial evidence supporting the benefit. Corticosteroid use does not appear to provide a benefit and in some cases worsens symptoms. Further studies are needed on other treatments to determine definitive efficacy.[47]

CONCLUSION

Chronic autoimmune demyelinating neuropathies are heterogeneous in presentation and treatment response. CIDP is commonly misdiagnosed, resulting in inappropriate and potentially harmful treatments. Because of overlapping symptoms and clinical findings, electrophysiologic and other supportive data are necessary to confirm the diagnosis and guide appropriate treatment.

KEY POINTS

- **Treatment of typical CIDP and its variants is similar and includes IVIg, steroids, or plasma exchange as first-line induction and maintenance therapies.**
- **Transition from IVIg to subcutaneous immunoglobulin in the treatment of immune-mediated neuropathies can occur in a 1:1 dosing transition.**
- **Rituximab treatment appears to be the most effective treatment for patients with antiparanodal and antinodal antibody immune-mediated neuropathies.**
- **Several randomized controlled trials support the use of IVIg as a first-line treatment for multifocal motor neuropathy.**

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Autoimmune Axonal Neuropathies

By Jennifer A. Tracy, MD

ABSTRACT

OBJECTIVE: This article reviews autoimmune axonal neuropathies, their characteristic clinical features, disease and antibody associations, appropriate ancillary testing, treatment, and prognosis.

LATEST DEVELOPMENTS: In 2021, the American College of Rheumatology and the Vasculitis Foundation released new summary guidelines for the treatment of antineutrophil cytoplasmic autoantibody–associated vasculitides. In addition, novel autoantibodies have been recently identified; they are often paraneoplastic and associated with axonal neuropathies.

ESSENTIAL POINTS: Recognition of autoimmune axonal neuropathies is important because of the potential for effective treatment to either reverse deficits or slow the progression of disease. It is necessary to properly assess for associations with other systemic disorders (eg, systemic vasculitis, connective tissue disease, neoplasm) so that adequate treatment for both neurologic and non-neurologic aspects of the disease can be initiated.

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Address correspondence to Dr Kelly Gwathmey, Virginia Commonwealth University, Department of Neurology, Short Pump Pavillion, 11958 W Broad St, Henrico, VA 23233, Kelly.Gwathmey@vcuhealth.org.

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INTRODUCTION

Among the wide range of causes of neuropathy, neurologists should be familiar with the autoimmune axonal neuropathies. In some cases, the immune-mediated component of these disorders can be responsive to immunotherapy, either with regression or stabilization of neuropathic symptoms and signs. In addition, many autoimmune axonal neuropathies occur in association with other systemic diseases, which themselves require treatment, such as systemic vasculitis, connective tissue diseases, and paraneoplastic disorders. Autoimmune axonal neuropathies can also occur in isolation, without associated systemic disorders, as in cases of nonsystemic peripheral nerve vasculitis.

These disorders and, when relevant, their accompanying systemic diseases are discussed in this article.

VASCULITIC NEUROPATHY

Vasculitis is a general term for disorders of inflammatory infiltration and destruction of blood vessel walls with subsequent downstream effects of tissue ischemia and damage; clinical manifestations depend on the organ systems involved. Vasculitis can be systemic or localized to specific organs and can affect

blood vessels of various sizes. It is sometimes associated with specific antibodies, which can be very helpful from a diagnostic and prognostic standpoint, but vasculitis can also be present without known antibody association, and tissue diagnosis can be especially important in these cases.

Vasculitis is a rare cause of neuropathy, but it can produce a very severe neuropathy, with a significant impact on function and quality of life. At the outset, one must determine if the vasculitic neuropathy is a manifestation of a systemic vasculitis or a vasculitis limited to peripheral nerves. This distinction is necessary for determining treatment strategy and appropriate prognostic counseling and for creating a comprehensive care team, including other specialists, for the most effective patient care. Peripheral neuropathy can be the presenting symptom of primary systemic vasculitis, with one study showing neuropathy as the initial presentation in 25% of cases (more frequently in eosinophilic granulomatosis with polyangiitis [EGPA] and polyarteritis nodosa [PAN]),[1] so periodic reassessment for systemic symptoms and signs is appropriate.

Vasculitic Neuropathy Classification

In 2010, the Peripheral Nerve Society published comprehensive guidelines regarding the classification of systemic and nonsystemic vasculitides (TABLE 4-1).[2] One of the main categories of systemic vasculitis is the primary systemic vasculitides, which are essentially forms of vasculitis not caused by a separate underlying medical condition or toxic exposure. This category includes large vessel vasculitis (giant cell vasculitis), predominantly medium vessel vasculitis (PAN), and predominantly small vessel vasculitis (microscopic polyangiitis, EGPA [ie, Churg-Strauss syndrome], granulomatosis with polyangiitis [GPA], essential mixed cryoglobulinemia [non–hepatitis C virus], and Henoch-Schönlein purpura). Another main category of the systemic vasculitides is secondary vasculitis, which is associated with more classical connective tissue disease, sarcoidosis, Behçet disease, infection, drugs, malignancy, inflammatory bowel disease, and hypocomplementemic urticarial vasculitis syndrome.[2] In 2012, new consensus criteria for the nomenclature of vasculitides placed a greater focus on pathologic findings.[3]

Vasculitic Neuropathy Clinical Presentation

The clinical presentation of vasculitic neuropathy can vary, but clues to vasculitis as a cause of neuropathy include an acute to subacute onset, both motor and sensory features (often including prominent neuropathic pain), profound sensory loss in isolation (sometimes with associated pseudoathetosis), and a multifocal presentation or progression. This distinctive clinical presentation is also described as "mononeuritis multiplex" in the literature. If patients present early in the disease course, one may not have the diagnostic advantage of seeing the development of multifocal features over time. Later in the disease course, the diagnosis of vasculitic neuropathy may be clouded by multiple overlapping mononeuropathies leading to a more symmetric length-dependent clinical examination. Usually, some asymmetry can still be detected, sometimes only in the degree of the deficit (clinically and electrophysiologically). Upper limb predominance and other non–length-dependent features should raise suspicion for vasculitis. A thorough review of systems is critical for diagnosis, with particular attention to systemic and constitutional symptoms. The presence or

KEY POINTS

- Vasculitis can be systemic or limited and can exclusively involve the peripheral nerves. Peripheral neuropathy can also be the presenting sign of primary systemic vasculitis.
- Clues for vasculitic neuropathy include subacute onset, mixed sensorimotor features, profound sensory loss, and multifocality.
- Later in the disease course, the diagnosis of vasculitic neuropathy may be clouded by multiple overlapping mononeuropathies leading to a more symmetric length-dependent clinical examination.

TABLE 4-1

Classification of Vasculitides Associated With Neuropathy[a]

I Primary systemic vasculitides

- 1 **Predominantly small vessel vasculitis**
  - a Microscopic polyangiitis
  - b Eosinophilic granulomatosis with polyangiitis
  - c Granulomatosis with polyangiitis
  - d Essential mixed cryoglobulinemia (non-hepatitis C virus [HCV])
  - e Henoch-Schönlein purpura
- 2 **Predominantly medium vessel vasculitis**
  - a Polyarteritis nodosa (PAN)
- 3 **Predominantly large vessel vasculitis**
  - a Giant cell arteritis

II Secondary systemic vasculitides associated with one of the following

- 1 **Connective tissue diseases**
  - a Rheumatoid arthritis
  - b Systemic lupus erythematosus
  - c Sjögren syndrome
  - d Systemic sclerosis
  - e Dermatomyositis
  - f Mixed connective tissue disease
- 2 **Sarcoidosis**
- 3 **Behçet disease**
- 4 **Infection (such as hepatitis B virus, HCV, human immunodeficiency virus [HIV], cytomegalovirus, leprosy, Lyme disease, human T-cell lymphotropic virus type I [HTLV-I])**
- 5 **Drugs**
- 6 **Malignancy**
- 7 **Inflammatory bowel disease**
- 8 **Hypocomplementemic urticarial vasculitis syndrome**

III Nonsystemic or localized vasculitis

- 1 **Nonsystemic vasculitic neuropathy (includes nondiabetic radiculoplexus neuropathy and some cases of Wartenberg migrant sensory neuritis)**
- 2 **Diabetic radiculoplexus neuropathy**
- 3 **Localized cutaneous or neuropathic vasculitis**
  - a Cutaneous PAN
  - b Others

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absence of fevers, chills, night sweats, and associated weight loss is important to assess, although significant weight loss is also associated with radiculoplexus neuropathy, a type of nonsystemic microvasculitis. One needs to assess for evidence of associated rheumatologic disease (including rash, arthritis and arthralgia, and sicca symptoms) and other organ system involvement such as lung, renal, and gastrointestinal disease. Antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitic neuropathy may be present at baseline with systemic symptoms (including arthralgia, arthritis, myalgia, fever, and weight loss) and cutaneous, mucous membrane, and otolaryngologic manifestations.[4] Risk factors for infectious or malignant disease or a history of drug use (medication as well as illicit drug use) and any temporal correlation with symptoms are also important parts of the patient's evaluation.

Vasculitic Neuropathy Diagnostic Evaluation

Laboratory studies for suspected vasculitic neuropathy include complete blood cell count with differential, comprehensive metabolic panel, antinuclear antibody, antibodies to extractible nuclear antigens, ANCAs (cytoplasmic and perinuclear), rheumatoid factor, cyclic citrullinated peptide antibodies, rheumatoid factor, sedimentation rate, C-reactive protein, cryoglobulins, complement, serum protein electrophoresis with immunofixation, and hepatitis B and C testing. Other infectious disease testing should be considered if the patient has suggestive systemic symptoms, a history of possible Lyme disease exposure, or an immunosuppressed state raising the suspicion for an infectious cause. Chest x-ray and urinalysis are generally obtained to screen for evidence of systemic disease.[2] Cytoplasmic and perinuclear ANCA testing has particular importance in the diagnosis of vasculitis; both forms of ANCA target cytoplasmic antigens in neutrophils and monocytes. The target of cytoplasmic ANCA is generally proteinase 3, and the target of perinuclear ANCA is generally myeloperoxidase.[5] Myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody is commonly associated with microscopic polyangiitis, and proteinase 3 antineutrophil cytoplasmic autoantibody is commonly associated with GPA.

MRI studies of nerves can be considered, particularly if a single nerve or nerve trunk is involved, mainly to rule out alternative etiologies such as an infiltrative process (eg, lymphoma, direct malignant extension into nerve, or sarcoidosis). Nerve conduction studies and EMG are critical for evaluation of suspected vasculitic neuropathy to both support the diagnosis and establish a baseline in case of planned treatment. Similar to the clinical evaluation, one of the main goals is to evaluate for multifocal nerve involvement and asymmetry; therefore, side-to-side comparisons are often very important. Given the frequent multifocality of presentation, the nerve conduction studies and EMG should be carefully designed to be sure clinically affected nerves are assessed. Again, if it is later in the disease course, a more symmetric length-dependent pattern may be seen on nerve conduction studies and EMG, but this should not dissuade the clinician from the possibility of vasculitis if the clinical history is one of stepwise progression of deficit.

Nerve biopsy is important in making the diagnosis in most cases of vasculitic neuropathy, although sometimes this is deferred when clinical evidence of vasculitis involving other organ systems is already known. If nerve biopsy is pursued, in most cases, biopsy of a distal sensory nerve is performed (sural,

KEY POINTS

- Myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody is commonly associated with microscopic polyangiitis.
- Proteinase 3 antineutrophil cytoplasmic autoantibody is commonly associated with granulomatosis with polyangiitis.
- For patients presenting with long-standing severe neuropathy, a history of step-wise progression should be queried because neurophysiology may only disclose nonspecific length-dependent findings.
- Nerve biopsy can be diagnostic in patients with suspected vasculitic neuropathy, but a clinically affected nerve must be selected for biopsy.

superficial peroneal sensory). However, because most vasculitic neuropathies are multifocal, one must be certain to biopsy a clinically affected nerve to improve diagnostic yield. Selection of an appropriate biopsy site is dictated by evidence of deficit on clinical examination and on nerve conduction studies. Less commonly, fascicular biopsy of a proximal nerve or nerve trunk could be considered, but these biopsies are for cases in which an alternative (usually infiltrative) process is being seriously considered. Fascicular biopsies (of a proximal nerve or a distal sensory nerve) are also less advisable when the strongest suspicion is for vasculitis. For a diagnosis of vasculitis, whole sural nerve biopsy is preferred because the interstitium-residing blood vessels are more consistently present and assessable for vasculitic changes. Additional biopsy of muscle along with nerve (eg, peroneus brevis and superficial peroneal nerve) is commonly performed, with one study showing a 27% improvement in the yield of definite vasculitis diagnosis.[6] The Peripheral Nerve Society published criteria for the diagnosis of pathologically definite, probable, and possible vasculitis (TABLE 4-2, TABLE 4-3, and TABLE 4-4).[2]

Vasculitic Neuropathies Associated With Systemic Vasculitis

Although many types of primary vasculitis have been identified, this article focuses on those most associated with peripheral nerve complications:

TABLE 4-2

Diagnostic Criteria for Pathologically Definite Vasculitic Neuropathy[a,b]

I Active lesion: nerve biopsy showing collection of inflammatory cells in vessel wall AND one or more signs of acute vascular damage

1 Fibrinoid necrosis;

2 Loss or disruption of endothelium;

3 Loss or fragmentation of internal elastic lamina;

4 Loss or fragmentation or separation of smooth muscle cells in media (can be highlighted with anti–smooth muscle actin staining);

5 Acute thrombosis;

6 Vascular or perivascular hemorrhage; OR

7 Leukocytoclasia

II Chronic lesion with signs of healing or repair: nerve biopsy showing collection of mononuclear inflammatory cells in vessel wall AND one or more signs of chronic vascular damage with repair

1 Intimal hyperplasia;

2 Fibrosis of media;

3 Adventitial or periadventitial fibrosis; OR

4 Chronic thrombosis with recanalization

III No evidence of another primary disease process that can mimic vasculitis pathologically, such as lymphoma, lymphomatoid granulomatosis, or amyloidosis

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[b] Presence of a chronic lesion does not exclude active vasculitis (vasculitides are usually segmental and multifocal, producing lesions of different ages in the same tissue or end organ).

microscopic polyangiitis, GPA, EGPA, and PAN. TABLE 4-5[7-13] reviews the typical clinical presentations and antibody associations of systemic vasculitides associated with vasculitic neuropathies. CASE 4-1 demonstrates a typical presentation.

Treatment of Systemic Vasculitic Neuropathy

In 2021, the American College of Rheumatology and the Vasculitis Foundation published guidelines for the management of ANCA-associated vasculitis.[14] Their recommendations include the use of glucocorticoids and rituximab for remission induction in active severe GPA or microscopic polyangiitis because of the noninferiority of rituximab to cyclophosphamide for remission induction in a prior study,[15] as well as the side effect profile. They indicate that cyclophosphamide could be used if rituximab is contraindicated or not sufficiently effective. Separate recommendations are established for active nonsevere disease; the presence of mononeuritis multiplex is a qualifying organ-threatening condition, and as such would be in the severe category by definition. For patients with severe GPA or microscopic polyangiitis who have achieved disease remission with rituximab or cyclophosphamide, the American College of Rheumatology and the Vasculitis Foundation conditionally recommended the use of maintenance rituximab. If rituximab is not an option for medical or financial reasons, they indicate that azathioprine and methotrexate are equally effective for the maintenance of remission. They

Diagnostic Criteria for Pathologically Probable Vasculitic Neuropathy[a] TABLE 4-3

I Pathologic criteria for definite vasculitic neuropathy not satisfied (see TABLE 4-2); AND

II Predominantly axonal changes; AND

III Perivascular inflammation accompanied by signs of active or chronic vascular damage (as defined in TABLE 4-2); OR

Perivascular or vascular inflammation plus at least one additional class II or III pathologic predictor of definite vasculitic neuropathy[b]

1. Vascular deposition of complement, IgM, or fibrinogen by direct immunofluorescence;
2. Hemosiderin deposits (Perls stain for iron);
3. Asymmetric or multifocal nerve fiber loss or degeneration;
4. Prominent active axonal degeneration; or
5. Myofiber necrosis, regeneration, or infarcts in concomitant peroneus brevis muscle biopsy (not explained by underlying myopathy)

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[b] Additional alterations used by some investigators as supportive of vasculitis but lacking in adequate evidence (more study required):

1. Neovascularization (class II and III evidence suggests that this finding is probably not a predictor of vasculitis);
2. Endoneurial hemorrhage (one negative class II study; one positive class III study);
3. Focal perineurial inflammation, degeneration, thickening (only class IV evidence);
4. Injury neuroma, microfasciculation (only class IV evidence); AND
5. Swollen axons filled with organelles (one negative but nonconvincing class II study) and other experimentally demonstrated axonal changes of acute ischemia, such as attenuated axons, flattened myelin profiles, tubular profiles, and axonal cytolysis.

further state that mycophenolate treatment has a higher relapse rate than azathioprine,[16] and so it should be considered only for those who cannot receive or tolerate azathioprine, methotrexate, or rituximab as a maintenance therapy. The guidelines proposed that the length of glucocorticoid use should be determined on a case-by-case basis.

Glucocorticoids (either oral or IV) in conjunction with either rituximab or cyclophosphamide are recommended for remission induction in active severe EGPA. If a patient with active severe EGPA then enters remission on cyclophosphamide, the American College of Rheumatology and the Vasculitis Foundation conditionally recommend maintenance therapy with methotrexate, azathioprine, or mycophenolate mofetil; however, rituximab could be used if a patient goes into remission with the use of rituximab or has contraindications to the other medications listed. Similar to GPA and microscopic polyangiitis, the length of use of glucocorticoids should be determined on a case-by-case basis.[14]

Polyarteritis nodosa is typically managed with corticosteroids and cyclophosphamide, although antiviral treatment is used in hepatitis B–associated cases.[17]

Cryoglobulinemic neuropathy is another type of vasculitis occurring secondary to the presence of circulating immunoglobulins, which precipitate at low temperatures and can deposit in blood vessels and initiate a pathway of complement-dependent damage to the blood vessels. These immunoglobulins can be associated with infection, particularly in chronic hepatitis C; one study showed mixed cryoglobulins present in 56% of patients with a hepatitis C virus infection.[18] For further detail regarding findings and management of cryoglobulinemic neuropathy, refer to the article "Paraproteinemic Neuropathies" by Said R. Beydoun, MD, FAAN, and Leila Darki, MD,[19] in this issue of *Continuum*.

In most cases, the treatment of systemic vasculitis, even with neuropathic manifestations, is directed by rheumatologists because of the multisystem or potentially multisystem involvement. One study assessing treatment outcomes based on ANCA type indicated that patients with proteinase 3-ANCA–associated vasculitis were more likely to have complete remission at 6 months if they were treated with rituximab than if they were treated with cyclophosphamide followed by maintenance azathioprine; no significant difference was seen in the rates of complete remission between the groups in myeloperoxidase-ANCA–associated vasculitis.[20] Another study found that 35% of 40 patients with ANCA-associated vasculitic neuropathy at baseline had complete resolution

TABLE 4-4 **Diagnostic Criteria for Pathologically Possible Vasculitic Neuropathy[a]**

- **I** **Pathologic criteria for definite or probable vasculitic neuropathy not satisfied; AND**
- **II** **Predominantly axonal changes; AND**
- **III** **Inflammation in vessel wall without other signs of definite vasculitic neuropathy; OR One or more signs of active or chronic vascular damage or pathologic predictors of definite vasculitic neuropathy (as defined in TABLE 4-2), without vessel wall or perivascular inflammation**

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Systemic Vasculitides Associated With Vasculitic Neuropathies

TABLE 4-5

Systemic vasculitis	Size of involved vessels	Organ involvement	Peripheral neuropathy frequency	Antibody association	Other comments
Microscopic polyangiitis	Small-sized blood vessels	Renal involvement in most including focal segmental necrotizing glomerulonephritis and glomerular crescents; pulmonary involvement; skin findings (palpable purpura); abdominal pain; hematologic disorders (anemia, leukocytosis, thrombocytosis)	Approximately 50% develop neuropathy	Myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody (ANCA) most common; cytoplasmic ANCA reported[7]; may be antibody-negative	Granulomas not seen
Granulomatosis with polyangiitis (GPA)	Small- and medium-sized blood vessels	Early respiratory involvement; renal disease; hematologic disorders (thrombocytosis, low hemoglobin)	Approximately 25% develop neuropathy	Proteinase 3-cytoplasmic ANCA in 80%; myeloperoxidase–perinuclear ANCA is rare	Neuropathy develops later in the GPA course and is milder[8]
Eosinophilic GPA (EGPA)	Small- and medium-sized blood vessels	Adult-onset asthma present in up to 91%[9]; peripheral eosinophilia	46-60% develop neuropathy, and it may be the presenting symptom[2,9]	Myeloperoxidase–perinuclear ANCA is the most common; many patients are antibody-negative[10]	Myeloperoxidase-ANCA–positive patients are more likely to have vasculitis on nerve biopsy[11]; myeloperoxidase-ANCA–negative patients may have more eosinophils in the blood vessel lumens[11]
Polyarteritis nodosa (PAN)	Small- and medium-sized arteries	Kidney (renal artery aneurysms); skin findings (livedo reticularis, cutaneous necrosis, nodules); abdominal pain; joint abnormalities; hematologic disorders (anemia, leukocytosis, thrombocytosis)	Peripheral neuropathy in approximately 50%	ANCA negative	PAN may occur in the context of hepatitis B[12]; hepatitis B–associated PAN has a higher rate of peripheral neuropathy[13]

within 6 months of treatment of their disease and that all of the patients had remission from active neuropathy within 9 months.[4]

Nonsystemic Vasculitic Neuropathy and Neuropathy Due to Localized Vasculitis

Nonsystemic vasculitis limited to peripheral nerves can present in several ways. Like systemic vasculitis, it can present with a stepwise progression of neurologic deficits but can clinically appear symmetric or nearly so as the areas involved by multiple nerves coalesce. Asymmetry, particularly in the early stages of disease, can often be detected on clinical examination or electrophysiologically (with nerve conduction studies and EMG). Some forms of nonsystemic peripheral nerve vasculitis involve very restricted areas of nerves and some are monophasic, which is discussed later in this article. Several connective tissue diseases can be linked to vasculitic neuropathy, and that subset of disease is also discussed in a later section.

The Lumbosacral Radiculoplexus Neuropathies

The radiculoplexus neuropathies are vasculitic neuropathies limited to nerves and tend to have a better prognosis than many other forms of immune-mediated axonal neuropathies. Diabetic lumbosacral radiculoplexus neuropathies (identified by variable names in the medical literature, including diabetic amyotrophy and proximal diabetic neuropathy) are an uncommon but usually severe neuropathy; for more information on this disorder, refer to the article

CASE 4-1

A 42-year-old woman developed pain and numbness on the dorsum of her left forearm, with associated wrist and finger drop, over a 3-day period. She initially attributed it to a sleeping position, but 1 month later, she developed right-sided footdrop with pain and numbness along the outer surface of her calf. She sought clinical attention, and an extensive review of systems revealed that she had been diagnosed with adult-onset asthma 2 years before. Laboratory testing was positive for myeloperoxidase–antineutrophil cytoplasmic autoantibody (ANCA) and peripheral eosinophilia. Nerve conduction studies and EMG showed evidence of a right peroneal neuropathy, without evidence of conduction block or focal slowing, and a left radial neuropathy. Right superficial peroneal nerve biopsy showed evidence of lymphocytic infiltration and destruction of blood vessel walls, multifocal nerve fiber loss, and hemosiderin deposition, consistent with a vasculitic process. She was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA). A rheumatologic consultation was obtained for collaborative treatment, and corticosteroids and rituximab were initiated.

COMMENT

The presence of asthma, myeloperoxidase-ANCA, and eosinophilia, in conjunction with an asymmetric axonal neuropathic process, is very typical for EGPA. Given the evidence of systemic vasculitis, careful coordination of care with a rheumatologist for ongoing treatment and monitoring is critical.

"Diabetic Neuropathies" Melissa A. Elafros, MD, PhD, and Brian C. Callaghan, MD, MS, FAAN,[21] in this issue of *Continuum*.

Lumbosacral radiculoplexus neuropathy can also occur in patients who do not have diabetes but have similar clinical, nerve conduction study and EMG, and CSF findings, as well as nerve biopsy findings diagnostic or supportive of microvasculitis. The progression, prognosis, and treatment do not significantly differ in these patients, and recovery is often incomplete.[22]

Postsurgical Inflammatory Neuropathy

Another form of inflammatory axonal neuropathy is postsurgical inflammatory neuropathy. Although many mechanisms can be responsible for neuropathy that develops in a surgical or postsurgical context, such as focal compression and stretch injuries, often related to positioning or direct trauma to nerves, a subset of patients develops an inflammatory neuropathic process. A study of 33 patients with postsurgical neuropathy, 21 of whom had nerve biopsies showing inflammation and an additional 12 with clinically suspected postsurgical inflammatory neuropathy, showed a focal or multifocal neuropathy in 79% and a diffuse neuropathy in 21%. The most common preceding procedures were orthopedic and abdominal or pelvic surgeries.[23]

When considering traction or compression injury versus an inflammatory cause, a delay between time of surgery and onset of symptoms and progressive symptoms in the hours and days after surgery are both consistent with an inflammatory cause. In an analysis of the biopsy-proven cases, all patients presented acutely or subacutely, with a median symptom onset of 2 days (but up to 30 days) after surgery; the most common clinical presentation was lumbosacral radiculoplexus neuropathy (in 10 of 21 patients), but brachial plexus neuropathy, sciatic mononeuropathy, polyradiculoneuropathy, phrenic neuropathy, and combinations of neuropathy patterns were also seen. Nerve conduction studies and EMG showed an axonal process in the affected limbs; two-thirds of those in whom CSF analysis was performed showed an elevated protein level. MRI, when performed, was abnormal in the clinically affected distribution of roots, plexus, or peripheral nerves, with increased T2 signal and varying degrees of nerve enlargement in all; only 1 of 12 patients who received gadolinium showed nerve enhancement. Eighteen of 21 nerve biopsies performed demonstrated evidence of ischemic injury. All the nerve biopsies had epineurial perivascular inflammatory collections, and 12 of 21 also showed endoneurial perivascular inflammation; 15 of the biopsies showed features of microvasculitis. Long-term, detailed follow-up available for 13 patients showed significant improvement in Neuropathy Impairment Scores in those receiving and not receiving immunotherapy.[23]

Neuralgic Amyotrophy

Neuralgic amyotrophy (ie, Parsonage-Turner syndrome) is a disorder that typically presents with an acute onset of unilateral shoulder pain, usually resolving within a couple of weeks, but evolves into weakness or sensory deficits of the affected limb. The timing of the onset of the weakness is often difficult to clearly ascertain because severe pain often impedes movement of the limb. Typically, patients have no associated constitutional symptoms. The most commonly involved regions are the upper trunk of the brachial plexus, suprascapular nerve, long thoracic nerve, and axillary nerve.[24] Risk factors for

KEY POINTS

- Myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody, asthma, and eosinophilia are commonly associated with eosinophilic granulomatosis with polyangiitis.

- Polyarteritis nodosa and associated neuropathy can develop in the context of hepatitis B infection.

- Although radiculoplexus neuropathies are more commonly present in patients with mild diabetes, a nondiabetic form also exists. Nondiabetic lumbosacral radiculoplexus neuropathy is usually monophasic with gradual, sometimes incomplete recovery.

- Although postsurgical neuropathies are often related to stretch or direct trauma, they are sometimes inflammatory.

- Neuralgic amyotrophy is usually monophasic; when repeated events occur, suspicion should be raised for hereditary brachial plexus neuropathy.

the development of neuralgic amyotrophy include recent viral illness or vaccination, as well as recent surgery.[25] It is important to rule out alternative diagnoses such as cervical radiculopathy or orthopedic injury; nerve conduction studies and EMG are very helpful in this regard, although they can be misleadingly unremarkable if performed too early in the course of the disease. It is also important to note that not all the nerve components commonly involved are studied on routine nerve conduction studies and EMG of the upper limb, so a carefully designed study based on the patient's clinical findings and deficits is critical. In addition, the presence of superimposed or preexisting mononeuropathies, such as carpal tunnel syndrome or ulnar neuropathy, can complicate localization. Given the predilection for the upper trunk of the brachial plexus in many cases, nerve conduction studies of bilateral lateral antebrachial cutaneous nerves (evaluating for significant asymmetry) can help confirm a postganglionic process. MRI of the cervical spine and brachial plexus is often useful in ruling out alternative diagnoses such as cervical radiculopathy or an infiltrative process in nerves. MRI and high-resolution ultrasonography are also valuable tools in the diagnosis of neuralgic amyotrophy as they frequently demonstrate nerve constriction and torsion and may demonstrate nerve enlargement.[26] Nerve biopsy of the brachial plexus in patients with neuralgic amyotrophy demonstrates prominent inflammatory infiltrates around epineurial or endoneurial vessels.[27] In most cases of neuralgic amyotrophy, nerve biopsy is not required or even desirable, and diagnosis can be made on the basis of clinical assessment, EMG, and other noninvasive modalities. Nerve biopsy in these cases should be reserved for instances of high suspicion of an alternative diagnosis that would lead to a change in management.

Generally, neuralgic amyotrophy is a monophasic process; in patients with recurrence, the rare syndrome of hereditary brachial plexus neuropathy (for which genetic testing is available for a *SEPTIN9* [previously *SEPT9*] variation) should be considered. Of note, a small study of nerve biopsies during attacks in patients with hereditary brachial plexus neuropathy showed prominent perivascular infiltrates in two of the four biopsies and neurogenic changes with limited inflammation in a third.[28] The fourth biopsy did not show neuropathic or interstitial abnormalities but was limited to a single fascicle, which limited the evaluation.[28]

Treatment of neuralgic amyotrophy is controversial, given its monophasic nature in most patients and the tendency for clinical improvement over time, with one study showing 89% of patients with full functional recovery at 3 years.[29] Although many clinicians opt for a short-term course of corticosteroids, evidence to support this treatment is limited,[30] and symptomatic strategies and physical therapy are mainstays for all patients significantly affected. More recently, because of the increased appreciation of hourglass-like constrictions as part of the pathophysiology of neuralgic amyotrophy, peripheral nerve surgical exploration may be considered after a 3-month interval of conservative management.[26]

Wartenberg Migratory Sensory Neuritis

Wartenberg's migratory sensory neuritis is considered a very rare condition and is characterized by sensory findings and symptoms confined to cutaneous nerves. The typical presentation is a rapid-onset of sensory symptoms, pain or numbness or both, and in one or multiple nerve distributions and can be recurrent over time. A frequently noted feature is pain in a specific nerve

distribution elicited by a position that results in a stretch of the nerve. One study that prospectively followed 12 patients indicated that, at the time of evaluation, a median of six skin areas were affected and that 75% of the patients had at least one associated nerve conduction study abnormality. It also reported that, after a mean disease duration of 7.5 years, three patients had a resolution of symptoms, five patients had residual numbness but no pain, three patients had residual numbness and pain, and one patient had developed a distal symmetric polyneuropathy.[31] Nerve biopsies have shown variable results, including inflammatory changes[32,33] and axonal degeneration with fascicular involvement suggestive of an ischemic process but without inflammation.[34] Data regarding immunotherapy responsiveness are very limited, with reports of nonresponse or nonsustained response.[32,33] However, these reports are difficult to interpret because of the rarity of the disease as well as the tendency to avoid immunotherapy given the relatively mild symptoms in many patients.

KEY POINT

- Between 5% and 20% percent of patients with Sjögren syndrome have some type of peripheral nervous system complication.

CONNECTIVE TISSUE DISEASE–ASSOCIATED NEUROPATHY

Many neurologic syndromes, both central and peripheral, are associated with connective tissue disease; this section focuses on peripheral nerve associations with connective tissue disease and its treatment.

Sjögren Syndrome

Sjögren syndrome is an autoimmune rheumatologic disorder that can occur in isolation or association with other rheumatologic diseases. It is typically characterized by severe sicca symptoms (eg, dry eyes, dry mouth) but can include other organ system dysfunction such as pneumonitis and pancreatitis, as well as peripheral neuropathy. It is often associated with elevated levels of anti-Ro/Sjögren syndrome A (SSA) and anti-La/Sjögren syndrome B (SSB) antibodies and with lymphoplasmacytic infiltration on minor salivary gland biopsy. It is estimated that between 5% and 20% percent of patients with Sjögren syndrome have some type of peripheral nervous system complication.[35,36] The peripheral nervous system associations can be varied, including sensory neuronopathy (ie, dorsal root ganglionopathy), sensorimotor peripheral neuropathy, pure sensory neuropathy (large or small fiber), vasculitic neuropathy, and isolated autonomic dysfunction. One study of 92 patients with Sjögren syndrome and neuropathy ranked the most common types of neuropathy in the following order: (1) sensory ataxic neuropathy (36 of 92), (2) painful sensory neuropathy without sensory ataxia (18 of 92), (3) trigeminal neuropathy (15 of 92), (4) multiple mononeuropathy (11 of 92), (5) multiple cranial neuropathy (5 of 92), (6) radiculoneuropathy (4 of 92), and (7) autonomic neuropathy (3 of 92).[37]

Sensory neuronopathy or ganglionopathy is one of the most severe forms of neuropathy associated with Sjögren syndrome, often with sensory ataxia resulting in significant disability. The typical clinical presentation is illustrated in CASE 4-2. These patients typically have severe predominantly large fiber sensory loss with impaired proprioception and absent reflexes.

Deficits are often not length dependent. Pain can also be present, occurring in one-half of patients with Sjögren syndrome–associated sensory neuronopathy, as shown in one study.[37] Nerve conduction studies and EMG can be very helpful, showing markedly reduced or absent sensory nerve action potentials and preservation of motor responses, which are often accompanied by abnormal somatosensory evoked potentials. In some cases, MRI shows abnormalities in

either the posterior columns of the spinal cord or the dorsal root ganglia themselves. In a large study by Mori and colleagues,[37] 31 patients with this phenotype had sural nerve biopsy, with the typical finding of reduced myelinated fiber density; however, 9 of the 31 patients had mild perivascular lymphocytic infiltrate, and 6 of the patients had chronic vasculitis of epineurial arterioles. This series included an autopsy case of a patient with sensory ataxic neuropathy. The patient had pathologic findings of severe large sensory neuron and sympathetic neuron loss, with multifocal T-cell invasion of the dorsal root and sympathetic ganglion, perineurial space, and vessel walls in the nerve trunks. Diagnostic criteria for sensory neuronopathy, incorporating clinical and electrodiagnostic features, have been published.[38]

Sensorimotor and sensory neuropathies are very common in patients with Sjögren syndrome, with varying degrees of severity from significant weakness and sensory loss to mild burning sensations in the feet. Nerve conduction studies and EMG can help determine the extent of large nerve fiber involvement and typically show an axonal pattern. Dedicated small nerve fiber testing, although often less available, can be very helpful in establishing the presence and degree of small fiber dysfunction. This can be particularly helpful in patients with only positive sensory symptoms, no clear sensory deficit, and normal electrodiagnostic studies and when there may be confusion between the presence

CASE 4-2

A 24-year-old woman with no prior medical history developed numbness in both hands over the course of 6 weeks, which was followed by asymmetric numbness in both lower extremities, distal worse than proximal. She had difficulty walking and a tendency to stumble, especially on uneven surfaces. She denied any associated weakness or pain. With further questioning, she reported that she had switched from her contact lenses to glasses, because her eyes felt drier, and she had started to drink more water than usual. Clinical examination showed normal strength and patchy areas of severe sensory loss, including impaired proprioception and sensory ataxia, and she was areflexic. Nerve action studies and EMG showed absent sensory nerve action potentials with normal motor conduction studies and needle examination, consistent with a sensory ganglionopathy. Serology was positive for antinuclear antibodies, anti-Ro/Sjögren syndrome A (SSA), and anti-La/Sjögren syndrome B (SSB), and lip biopsy showed evidence of lymphoplasmacytic infiltration. The patient was diagnosed with Sjögren syndrome with associated sensory neuronopathy. Treatment trials were attempted with corticosteroids and then with IV immunoglobulin (IVIg), which resulted in stabilization but no clinical improvement of her neurologic findings.

COMMENT

Sensory ganglionopathy is a common peripheral nervous system manifestation of Sjögren syndrome. Careful attention should be given to the evaluation of sicca symptoms, which can be subtle or attributed to other causes.

of small fiber neuropathy or pain from local factors such as plantar fasciitis or arthritis. Useful small nerve fiber tests may include components of quantitative sensory testing, autonomic reflex screening, thermoregulatory sweat testing, and skin biopsy assessing epidermal nerve fiber density. A study in which eight patients with a nonataxic painful sensory Sjögren syndrome neuropathy had MRI of the spine showed that three had minimal T2 hyperintensities in the posterior columns (although less prominent than in the ataxic form); so, although this finding is present in the minority of these patients, it could be a helpful clinical clue.[37] Nerve biopsies in patients with painful sensory neuropathy typically show predominant small fiber loss, with only one in nine patients in one series showing perivascular cell invasion.[37]

The multiple mononeuropathy phenotype of Sjögren syndrome neuropathy is generally more recognizable as an immune-mediated process, given its asymmetry and stepwise progression. Nerve conduction studies and EMG are generally consistent with axonal loss in the distribution of the nerves affected. Nerve biopsy generally shows axonal damage; one study of eight sural nerve biopsies in patients with Sjögren syndrome neuropathy showed five patients with pathologic findings of vasculitis and six patients with perivascular cell invasion.[37] It is very important in this phenotype to select a clinically affected nerve if biopsy is pursued. If the sural nerve is clinically or electrophysiologically involved, it can be a useful biopsy site because of its ease of biopsy and lack of motor function and because good normative data can be found. If the sural nerve is clinically unaffected, alternative sites of nerve biopsy should be considered (with careful consideration of the risks and benefits).

Treatment in these patients is generally related to the severity of disease as well as the rate of progression. For mild cases with pain predominance, treatment requires only symptomatic therapy with neuropathic pain agents. For more severe or progressive cases, immunotherapy trials should be considered (often in conjunction with neuropathic pain agents). It is likely patients will already be on immunotherapy or have immunotherapy planned by their rheumatologist for their primary disease, so coordination of care is important. The data vary regarding clinical response to immunotherapy in Sjögren syndrome neuropathy, and the response depends to some degree on the phenotype.

Generally, sensory neuronopathy tends to not respond well to immunotherapy, although this is attempted in most cases given the severity of disability associated with this form of neuropathy. The characteristic lack of response to immunotherapy in patients with sensory neuronopathy may reflect the very brief 8-month treatment window during which the disease may be stabilized.[39] If sensory neuronopathies are treated aggressively even earlier, within approximately 2 months, improvement may be possible. A study of IV immunoglobulin (IVIg) given to five patients with severe chronic ataxic sensory neuronopathy in Sjögren syndrome reported a significant neurologic improvement in four patients.[40] However, another study of IVIg in Sjögren syndrome neuropathy showed improvements in only two of nine patients with ataxic neuropathy and a worsening of symptoms in four patients over that same interval.[41] The study did note improvement or stabilization in the nine patients treated who had either sensorimotor or nonataxic sensory neuropathy.[41] One study assessing the use of prednisone or IVIg in sensory ataxic neuropathy showed a steroid response rate of 18% and an IVIg response rate of 23% 1 month after treatment.[37] The authors indicated that patients with multiple

KEY POINTS

- **Sjögren syndrome is associated with a wide array of neuropathic complications, most characteristically a sensory neuronopathy. Treatment responsiveness of Sjögren neuropathy is variable, and results of treatment are poor in cases of sensory neuronopathy.**

- **Rheumatoid arthritis is associated with many types of structural nerve damage (eg, from cervical spine disease or carpal tunnel syndrome) in addition to inflammatory mechanisms.**

mononeuropathy and multiple cranial neuropathies had better responses to corticosteroids than those with other neuropathy types.[37] A retrospective review of 13 patients with Sjögren syndrome and sensory neuronopathy assessed responses to several immunotherapy treatments, and overall improvement rates were low, with better responses when improvement and stability were combined as good outcomes.[42] Either improvement or stability occurred in 75% of patients (12 of 16) treated with corticosteroids (5 of 16 had improvement), in 92% of patients (11 of 12) treated with mycophenolate mofetil (5 of 12 had improvement), 50% of patients (3 of 6) treated with IVIg (1 of 6 had improvement), 80% of patients (4 of 5) treated with cyclophosphamide (2 of 5 had improvement), 67% of patients (6 of 9) treated with hydroxychloroquine (1 of 9 had improvement). One patient was treated with tacrolimus, and another was treated with azathioprine; neither had a response to treatment. The one patient who improved with IVIg was also on other treatments (corticosteroids and mycophenolate mofetil) at the time. Although responses to each agent above were reported, many of the patients were on combination immunotherapy during the review period, so the response rates should not be interpreted as a response rate to that agent in isolation. The article also listed each patient's timeline and combinations of medications attempted over time, and the authors noted that, even with treatment, neurologic impairment increased over time.[42] A small study of rituximab used for patients with Sjögren syndrome and peripheral nervous system disease showed a 90% response rate (in neurologic improvement) in patients with associated cryoglobulins or vasculitis or both, but only a 29% response rate in patients with neither of those two features, at a 3-month follow-up.[43]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a type of inflammatory arthritis that can also have peripheral nervous system manifestations; however, it is important to remember that nerve complications may not be primarily immune-mediated but secondary to the structural effects of the arthritis. Entrapment mononeuropathies are common in RA and should be treated the same as in patients who do not have RA. Cervical spondylosis and synovitis and atlantoaxial disease can also occur in patients with RA, and when these patients present with sensory symptoms, they should be carefully assessed for myelopathic signs and findings of upper extremity predominance, which could suggest cervical spine or cord disease. Sensorimotor peripheral neuropathy can also be present in patients with RA, and a study assessing these patients with and without neuropathy for potential risk factors showed no relationship with age, sex, or disease duration.[44] However, another study from Italy showed age as a risk factor for neuropathy in patients with RA, with a prevalence higher than expected when compared with the older adult Italian population.[45]

One study clinically and electrophysiologically evaluated 108 patients with RA for evidence of neuropathy, and in 23 cases, sural nerve biopsy was performed. In this study, 57.4% of patients had electrophysiologic findings of neuropathy (85.5% with pure sensory or sensorimotor axonal neuropathy, including seven patients with mononeuritis multiplex, and 14.5% with demyelinating neuropathy). Most of the neuropathies detected electrophysiologically were subclinical, with 75% of these having no clinical signs or symptoms of neuropathy. No correlation was found between the presence of neuropathy and

the duration of rheumatologic disease, rheumatoid factor seropositivity, or joint erosions or deformities. Some patients (10.1%) had carpal tunnel syndrome. On sural nerve biopsy, 11 of 23 the nerves were reported as normal; a minority of biopsies showed each of the following features: perivascular inflammatory infiltrates, perineurial thickening, amyloid deposition, and loss of myelinated fibers; only a single biopsy showed necrotizing vasculitis.[46] Generally, when evidence supports an immune-mediated process, immunotherapy is used to a varying degree depending on the severity of the underlying neuropathy. The incidence of rheumatoid vasculitis is reported to be decreasing over time, likely secondary to better options for the treatment and control of RA, but when present, it has a poor prognosis even with aggressive treatment with agents such as corticosteroids and cyclophosphamide.[47,48] Tumor necrosis factor α inhibitor therapy in patients with RA can also produce various types of peripheral neuropathy (often demyelinating) as a side effect, so this also needs to be considered a potential cause of neuropathy in patients with RA.[49]

KEY POINTS

- Tumor necrosis factor α inhibitor therapy for rheumatoid arthritis may trigger the development of neuropathy.
- Systemic lupus erythematosus may be associated with an axonal, asymmetric, or symmetric sensory or sensorimotor polyneuropathy. Many patients with systemic lupus erythematosus and polyneuropathy may have alternative causes for their polyneuropathy.
- Paraneoplastic neuropathies usually present acutely to subacutely and are often asymmetric. Antineuronal nuclear antibody type 1 (ANNA-1; anti-Hu), collapsin response mediator protein-5 (CRMP-5; also known as *anti-CV2*), and amphiphysin antibodies are among the most common paraneoplastic autoantibodies associated with neuropathy.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) can have accompanying neurologic symptomatology, more commonly involving the central nervous system. Peripheral nervous system dysfunction is less common but can have a significant impact on quality of life. A review of 1533 patients in a lupus clinic registry reported that 13.5% of the patients had a peripheral nervous system condition; however, this was determined by record review, so it may underestimate subclinical cases.[50] Patients with peripheral nervous system disease were older and more commonly had central nervous system involvement than the patients who had SLE without neuropathy. The most common peripheral presentation was a peripheral polyneuropathy (36.7% with sensory and 18.8% with sensorimotor symptoms); less common manifestations included cranial neuropathy, mononeuropathy, and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), and 9.2% of the patients had mononeuritis multiplex. The majority of patients had an asymmetric presentation.

When nerve conduction studies were performed on these patients, the findings in most (more than three-quarters of the patients) were that of an axonal neuropathy. In the 10 patients for whom nerve biopsy was performed, all showed perineurial inflammation, 2 showed axonal degeneration, and 1 showed demyelination. The authors did note in their review of clinical information that many patients had alternative reasons for their peripheral nervous system condition and only 8% of the total group surveyed in their registry were felt to have SLE-related polyneuropathy or possible SLE-related polyneuropathy.[50] However, another study that assessed nerve conduction studies showed polyneuropathy in 21% of the patients with SLE compared with 6% in the age- and sex-matched control group.[51] Omdal and colleagues[52] were able to follow up nerve conduction studies in 20 patients with SLE and neuropathy after a 7-year period and found that, of 24 nerve conduction parameters, 33% of the patients showed a significant decline, but 67% were unchanged. Another study retrospectively assessed neuropathy outcomes in 38 patients with SLE with polyneuropathy who received immunomodulatory treatment at the time of their neuropathy diagnosis, all with glucocorticoids and 97.4% with other immunosuppressive agents (50% IV cyclophosphamide and 42.1%

azathioprine).[53] At a 1-year follow-up, 36.8% of the patients were reported to have complete remission and 55.2% had partial remission; 89.3% had complete or partial remission at a 5-year follow-up (of the 28 patients evaluated at that time point). A good treatment response was more common in patients who developed polyneuropathy early in their SLE course (less than 1 year of SLE).[53]

PARANEOPLASTIC NEUROPATHY

The understanding of paraneoplastic neuropathies has undergone significant evolution, with an expanding range of testing to better identify this entity. The most common presentation of paraneoplastic neuropathy is an acute to subacute onset of asymmetric sensory neuronopathy. However, it can have a diverse range of possible presentations, including but not limited to a symmetric sensorimotor peripheral neuropathy, sensory peripheral neuropathy, myeloneuropathy, focal neuropathies, motor neuronopathy, and primarily autonomic neuropathies.[54] Many neuropathies are specifically associated with hematologic malignancies and monoclonal gammopathies, which are discussed in the article "Paraproteinemic Neuropathies" by Said R. Beydoun, MD, FAAN, and Leila Darki, MD,[19] in this issue of *Continuum* and will not be further addressed here. With the focus on axonal neuropathies in this article, the discussion of demyelinating neuropathy will be very limited here. Refer to the articles "Guillain-Barré Syndrome" by Ali A. Habib, MD, and Waqar Waheed, MD,[55] and "Chronic Immune-Mediated Demyelinating Neuropathies" by Karissa Gable, MD,[56] in this issue of *Continuum*.

Paraneoplastic neuropathy can have many different presentations, although the acute to subacute onset is an important clue to this diagnosis. The known presence of a cancer type (eg, small cell lung cancer) that is more frequently linked to paraneoplastic neurologic disease is helpful, but in many cases, the neurologic symptoms are the initial presentation, and the associated malignancy is found during the workup. The most commonly noted antibodies associated with paraneoplastic neuropathy are antineuronal nuclear antibody type 1 (ANNA-1; anti-Hu), collapsin response mediator protein-5 (CRMP5; also known as *anti-CV2*), and amphiphysin antibodies. The broad range of antibody associations including microtubule-associated protein-1B (MAP1B)–IgG, leucine-rich glioma inactivated (LGI1) antibodies, contactin-associated proteinlike 2 (CASPR2) antibodies, neuronal intermediate filament (NIF), and leucine zipper 4 (LUZP4) are included in TABLE 4-6.[57-63] It is not uncommon for patients to be positive for more than one paraneoplastic antibody, which can be helpful for better characterization of the illness, as well as prediction of underlying malignancy. In addition, many of the paraneoplastic autoantibodies are linked to more than one definable neurologic syndrome, so paraneoplastic autoantibody panel testing rather than single antibody testing is generally recommended. Different paraneoplastic antibodies are associated with different frequencies of neoplasm, as well as different types of neoplasm, so identification of a specific antibody can help with formulating a cancer screening plan.[64]

ANNA-1 (anti-Hu) is an intracellular antigen most abundant in nuclei and is present widely in central and peripheral nervous system neurons.[65] An early large study of 162 patients who were ANNA-1 positive showed that 81% were found to have small cell lung carcinoma during the period of follow-up (and of interest, 17 patients had at least one additional neoplasm); 97% of the small cell lung cancer diagnoses were made after the onset of neurologic symptoms.[66] This emphasizes the importance of careful cancer screening and continuing the search

for small cell lung cancer even if a separate malignancy has been identified. The neurologic findings in this series were most commonly neuropathy, typically sensory and mixed sensorimotor neuropathy, although multiple other types of neuropathy were found in antibody-positive patients. Central nervous system findings could also be present, including cerebellar ataxia and limbic encephalitis, and gastrointestinal dysmotility was seen in some patients. CSF abnormalities were common in these patients and could be seen even when only signs of peripheral nervous system involvement were present. None of the patients for whom clinical data regarding treatment (corticosteroids, IVIg, plasma exchange, or cyclophosphamide) were available had benefit, which is consistent with other data.[67] A retrospective study of 20 patients with anti-Hu neuropathy showed that clinically the neuropathy was sensory in 70% of patients and sensorimotor in 25%, and only 1 patient had pure motor involvement.[68] Sixty-five percent of these patients had symmetric symptoms, and 55% had a subacute onset. Electrophysiologic evaluation with nerve conduction studies of 272 nerves showed an axonal pattern in 46.9% of nerves and an axonal and demyelinating pattern in 18.3% of nerves. Most patients with a clinically sensory-only pattern did have some degree of motor conduction abnormalities electrophysiologically.[68] CASE 4-3 illustrates a typical presentation.

CRMP-5 antibodies (anti-CV2) are associated with peripheral neuropathy. They can also be found in the setting of other neurologic paraneoplastic syndromes including encephalitis, cerebellar ataxia, myelopathy, optic neuritis,

Less Common Paraneoplastic Antibodies Associated With Peripheral Neuropathies TABLE 4-6

Paraneoplastic antibody	Cancer association	Nervous system manifestations	Other comments
Microtubule-associated protein 1B (MAP1B)	Usually lung cancer[57]	Peripheral neuropathy in 53%[57]; painless polyradiculoneuropathy; symmetric, subacute-to-chronic sensory neuronopathy	50% in a small series responded to immunotherapy[58]
Leucine-rich glioma inactivated 1 (LGI1)	Cancer is more common in double seropositive patients (LGI-IgG and CASPR2-IgG)[59]; thymoma is most common	Autoimmune encephalitis or epilepsy; neuropathic pain, neuropathy, neuromyotonia	Serum testing is more sensitive than CSF testing; usually responsive to immunotherapy[59]
CASPR2 (contactin-associated proteinlike 2)	May be associated with thymoma and other cancers in a minority[60]	Limbic encephalitis; cognitive disorders; epilepsy; neuropathic pain; neuromyotonia	A minority of patients without underlying malignancy may respond to immunotherapy[60]
Neuronal intermediate filament (NIF)	Cancer is associated in approximately 75% of patients in one series[61]; most commonly carcinoma of neuroendocrine lineage	Ataxia; encephalopathy; myeloradiculoneuropathy	The majority (77%) of patients were immunotherapy responsive in one series[62]; may also be associated with infections and checkpoint inhibitor treatment
Leucine zipper 4 (LUZP4)	The vast majority will have seminoma, fewer than half are extratesticular[63]	Rhomboencephalitis; limbic encephalitis; motor neuronopathy; polyradiculopathy	Neurologic improvement is greater in those treated with both immunotherapy and cancer treatment[63]

retinitis, and vitreitis, among others. One study showed neuropathy in 42% of the 314 patients positive for CRMP-5 IgG, and in 96% of these patients, the neuropathy symptoms were present before cancer was diagnosed.[69] In the 69% of patients in whom a cancer was identified, the predominant type was small cell lung cancer (75%), followed by thymoma (15%), and rarely other malignancies. The most common peripheral neuropathic presentation was a painful, usually asymmetric polyradiculoneuropathy (present in 65% of the patients), and gastroparesis was also present in a significant minority of patients. For patients with nerve conduction data, the pattern was axonal. It was noted that 52% of patients received immunotherapy (oral or IV corticosteroids, IVIg, plasma exchange, cyclophosphamide, or mycophenolate), and only the IV corticosteroid use was associated with improvement or stabilization of Neuropathy Impairment Scores, although any corticosteroid use (IV or oral) was associated with improved neuropathic pain.[69]

Amphiphysin is a neuronal presynaptic cytoplasmic protein pertinent to inhibitory transmission and widely expressed in central and peripheral nervous system neurons; antibodies to amphiphysin can also be associated with paraneoplastic neurologic disease and have been found in some patients with stiff

CASE 4-3

A 55-year-old woman with cirrhosis (from hepatitis C virus infection) and prior tobacco use had an acute onset of patchy right chest and upper extremity pain, followed within a week by numbness in that same distribution, then by numbness involving her left upper extremity. Shortly thereafter, she developed progressive patchy lower extremity distribution numbness and gait instability, requiring the use of a wheelchair within a few months. She also described chronic lightheadedness.

Because of her chest symptoms, a chest x-ray was obtained and revealed a small lung nodule, later determined by biopsy to be an adenocarcinoma. She was treated with gamma knife radiation, which was felt to be curative. However, she had no change in her neurologic symptoms. Clinical examination showed severe loss of large fiber sensory modalities, ataxic gait, and pseudoathetosis, with absent muscle stretch reflexes. Evaluation included nerve conduction studies and EMG, which showed evidence of a sensory-predominant axonal peripheral neuropathy or ganglionopathy.

Autonomic reflex screening showed findings of distal postganglionic sympathetic sudomotor dysfunction and moderate orthostatic hypotension. Given her cancer history and clinical presentation, a serum paraneoplastic panel was ordered and revealed antineuronal nuclear antibody type 1 (ANNA-1) antibodies.

COMMENT

The typical presentation of ANNA-1 antibody–associated paraneoplastic neuropathy is sensory predominant and severe. A paraneoplastic mechanism should be considered in patients with subacute, progressive, asymmetric neuropathies even when an alternative underlying mechanism is present.

person syndrome who tested negative for glutamic acid decarboxylase 65 (GAD65).[70] In one review of patients with amphiphysin antibodies, 79% were found to have an associated malignancy, most commonly lung carcinoma (in 73% of the patients, almost exclusively small cell lung cancer) and less commonly breast carcinoma (25%).[71] Of 63 patients in this series with clinical information available, neuropathy was present in 33 (multiple types, most commonly sensory and sensorimotor), but multiple other neurologic manifestations were present, including 19 patients with encephalopathy, 18 with encephalitis with rigidity, and 17 with myelopathy. Most patients who had CSF evaluation had abnormal findings; the majority had lymphocytic pleocytosis and elevated protein levels. For patients evaluated at the authors' institution, they reported neurologic improvements in 9 patients treated for the malignancy and in 2 patients who received 5 days of IV methylprednisolone and no benefits in the patient who received IVIg and the 2 patients who received plasma exchange.[71] A later study identified 21 patients with amphiphysin antibodies only (no additional coexisting paraneoplastic antibodies) and neuropathy and found that 90% of them had a malignancy.[72] The most common in this series was breast adenocarcinoma (63%) followed by small cell lung cancer (22%) and diverse rarer malignancies. In this group, most patients had a chronic or subacute presentation of neuropathy, and a slight majority had a symmetric presentation. The most common presentation was polyradiculoneuropathy followed by sensory neuronopathy. A slight majority of patients with amphiphysin paraneoplastic neuropathies also had central nervous system disease in addition to neuropathy. Electrophysiologic studies showed evidence of an axonal neuropathic process. In this study, immunotherapy was significantly associated with improvement in the modified Rankin score, noting a particular benefit in patients receiving cyclophosphamide with either IV methylprednisolone or IVIg.[72]

CONCLUSION

It is important to recognize autoimmune axonal neuropathies because of the potential for both improvement or stabilization with immunotherapy in some types and the association with systemic disease, which requires management. The causes of autoimmune axonal neuropathies and their clinical presentations are diverse. The search for etiology can be challenging, especially with expanding knowledge of autoantibody associations, but the accuracy of diagnosis is important for treatment and prognosis.

IN MEMORIAM

The author of this article, Jennifer A. Tracy, MD, died September 26, 2023. She will be dearly missed by her family, friends, colleagues, and community.

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Diabetic Neuropathies

By Melissa A. Elafros, MD, PhD; Brian C. Callaghan, MD, MS, FAAN

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **This article provides an up-to-date review of the diagnosis and management of the most common neuropathies that occur in patients with diabetes.**

LATEST DEVELOPMENTS: **The prevalence of diabetes continues to grow worldwide and, as a result, the burden of diabetic neuropathies is also increasing. Most diabetic neuropathies are caused by hyperglycemic effects on small and large fiber nerves, and glycemic control in individuals with type 1 diabetes reduces neuropathy prevalence. However, among people with type 2 diabetes, additional factors, particularly metabolic syndrome components, play a role and should be addressed. Although length-dependent distal symmetric polyneuropathy is the most common form of neuropathy, autonomic syndromes, particularly cardiovascular autonomic neuropathy, are associated with increased mortality, whereas lumbosacral radiculoplexus neuropathy and treatment-induced neuropathy cause substantial morbidity. Recent evidence-based guidelines have updated the recommended treatment options to manage pain associated with distal symmetric polyneuropathy of diabetes.**

ESSENTIAL POINTS: **Identifying and appropriately diagnosing the neuropathies of diabetes is key to preventing progression. Until better disease-modifying therapies are identified, management remains focused on diabetes and metabolic risk factor control and pain management.**

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Address correspondence to Dr Brian C. Callaghan, 109 Zina Pitcher Pl, 4021 BSRB, Ann Arbor, MI 48109-2200, bcallagh@med.umich.edu.

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The institution of Dr Elafros has received research support from the National Center for Advancing Translational Sciences (UL1TR002240), the National Institute of Diabetes and Digestive and Kidney Diseases (P30-DK-02926 and P30-DK089503), and the National Institute of Neurologic Disorders and Stroke (5R25NS089450). Dr Callaghan has received personal compensation in the range of $500 to $4999 for serving as an editorial board member for the American Academy of Neurology, a consultant for Dynamed (EBSCO Industries, Inc), and a grant reviewer for the National Institutes of Health; in the range of $10,000 to $49,999 for serving as an expert witness for medicolegal work; and in the range of $50,000 to $99,999 for serving as an expert witness for the Vaccine Injury Compensation Program. The
Continued on page 1417

UNLABELED USE OF PRODUCTS/ INVESTIGATIONAL USE DISCLOSURE:
Drs Elafros and Callaghan discuss the unlabeled use of amitriptyline, lamotrigine, oxcarbazepine, and venlafaxine for the treatment of painful distal symmetric polyneuropathy.

INTRODUCTION

In 2021, more than half a billion people worldwide had either type 1 or type 2 diabetes.[1] Diabetes is one of the fastest-growing diseases; by 2045, 783 million people will be affected.[1] The burden of diabetes in the United States is equally bleak. Currently, more than 32 million Americans have diabetes, yet more than 1 in 10 individuals are unaware of their diagnosis.[1] Both type 1 and type 2 diabetes are well known for their causal association with peripheral neuropathies. These neuropathies result in significant physical and psychological morbidity, including disabling pain, depression, and worse quality of life, as well as increased medical costs.[2] Currently in the United States, more than $10 billion a year is spent on diabetic neuropathy and its associated complications.[3] Unfortunately, the prevalence of diabetic neuropathies will continue to rise as the burden of diabetes increases worldwide. Because of a lack of disease-modifying treatment for neuropathy, early diabetes diagnosis is essential to controlling factors that increase the risk of developing neuropathy. For patients with existing

KEY POINTS

- The prevalence of diabetic neuropathies will continue to grow as the burden of diabetes increases worldwide and, until disease-modifying treatments are identified, management is reliant on addressing factors that increase the risk of neuropathy and neuropathy-related complications.

- Neuropathy in diabetes can present with length-dependent, autonomic, focal, or generalized signs and symptoms.

- Distal symmetric polyneuropathy is the most common neuropathy in diabetes and presents with length-dependent numbness, tingling, and pain. Neurologic examination should include assessment of both large and small fiber function as small fiber nerves are often affected first in distal symmetric polyneuropathy.

- Any form of chronically elevated blood glucose has been associated with the development of distal symmetric polyneuropathy, including prediabetes.

- Screening for comorbid medical conditions among people with neuropathy is essential. In addition to diabetes duration and severity, metabolic syndrome components, in particular central obesity, are also associated with an increased risk of distal symmetric polyneuropathy among people with type 2 diabetes.

neuropathy, appropriate diagnosis and management are key to reducing the likelihood of developing complications, such as ulcer formation and lower extremity amputation.

The diabetic neuropathies present with a myriad of clinical signs and symptoms. This article focuses on the distinct clinical presentations of the most common forms of diabetic peripheral neuropathy, including distal symmetric polyneuropathy (DSPN), cardiovascular autonomic neuropathy, lumbosacral radiculoplexus neuropathy, and treatment-induced peripheral neuropathy. This article includes clinical descriptions of these disorders followed by sections on the diagnostic and management knowledge necessary to care for patients with diabetic neuropathies in conjunction with the patient's primary care provider or endocrinologist.

DISTAL SYMMETRIC POLYNEUROPATHY OF DIABETES

DSPN is the most frequent type of diabetic neuropathy. This chronic disorder presents with symmetric, altered sensation in the toes that spreads up the calves before beginning in the fingers and hands in a stocking-glove pattern.[4] Patients often report numbness, tingling, and altered sensation, including hyperalgesia. Symptoms vary dramatically among patients, and almost half endorse burning, stabbing, or aching pain.[5] Neurologic examination of these patients often reveals a combination of small and large nerve fiber involvement. Reduced sensation to pinprick and temperature suggests injury to unmyelinated and thinly myelinated small fibers, whereas decreased vibration, proprioception, and pressure occur after damage to myelinated large fibers. Weakness detected via confrontational or functional strength assessment can be seen in the setting of damage to myelinated motor fibers, although this is much less common than altered sensation.

DSPN occurs in approximately 30% of people with diabetes and is more common among people with type 2 diabetes than in those with type 1.[6] However, any form of chronically elevated blood glucose has been associated with DSPN development, including prediabetes, which is defined as a hemoglobin A_{1C} percentage between 5.7% and 6.4%.[7] Although patient age is a well-known risk factor for the development of neuropathy,[8] a DSPN prevalence as high as 22% has been reported among youth with type 1 diabetes, indicating that individuals of all ages are vulnerable to developing this complication.[9] Large population-based studies suggest that Black individuals are at higher risk for peripheral neuropathy after controlling for age and sex,[10] yet it is unclear whether this association is due to a higher diabetes prevalence among Black Americans or other factors. Additional diabetes-related risk factors associated with the development of DSPN include disease duration and severity, as measured by hemoglobin A_{1C}.[11] The risk of developing DSPN is further increased by comorbid medical conditions, in particular metabolic syndrome. Individuals are diagnosed with metabolic syndrome if they have at least three of the five following conditions: elevated fasting glucose, obesity, hypertension, elevated triglycerides, and low high-density lipoprotein.[12] Although central obesity has been repeatedly associated with the development of DSPN, a dose-response relationship may also occur between the number of metabolic syndrome components a patient has and the risk of DSPN.[11,12] Therefore, identification of metabolic syndrome components among patients with preexisting diabetes, or prediabetes, is warranted.

Diagnosis

DSPN is diagnosed via clinical history and neurologic examination (CASE 5-1). Electrodiagnostic testing is generally not recommended for clinically diagnosed DSPN in patients who have diabetes unless the patient has features that are atypical, such as rapid onset, non–length-dependent symptoms, asymmetry, or motor-predominant symptoms.[13] Although confirmation is generally not needed for clinical care, available tests include electrodiagnostic testing for those with large fiber symptoms and examination findings and skin biopsy for intraepidermal nerve fiber density for small fiber symptoms and examination findings. Nerve conduction studies will be consistent with axonal loss: low-amplitude responses with normal to slightly prolonged distal latencies and slowed conduction velocities. Sensory studies will be more affected than motor studies. Similar to electrodiagnostic testing, intraepidermal nerve fiber density is not recommended as a routine test. Intraepidermal nerve fiber density of a punch skin biopsy will show decreased density of small unmyelinated nerve fibers in the epidermal skin layer. Both modalities are good but not great

CASE 5-1

A 50-year-old woman with a 15-year history of type 2 diabetes was referred by her primary care physician to the neurology clinic. She presented with numbness and tingling in her legs. Her symptoms had begun almost a year ago as altered sensation in her toes, as if her socks were too tight, and had slowly spread up her feet to her ankles and the back of her legs. Sometimes she had zaps of shooting pain in her feet, which kept her from sleeping. She often had to keep her feet uncovered because she found the blankets irritating.

On examination, her body mass index was 30.5 kg/m^2. She had normal strength, reflexes, and coordination. Sensory examination showed intact proprioception at the great toes, sensation to vibration with a 128-Hz tuning fork was 5 seconds (10 seconds is normal), and she had decreased sensation to pinprick distally to just above the ankles. Her gait was normal.

A review of her medical records revealed an elevated hemoglobin A_{1C} for the past 20 years, which was most recently 6.4%. She also had elevated total cholesterol (220 mg/dL) and triglycerides (230 mg/dL).

COMMENT

This case illustrates a typical clinical presentation for a patient with distal symmetric polyneuropathy in the setting of diabetes with slow progression in symptoms over several months with an onset that cannot be clearly defined. Further diagnostic testing is unnecessary because of the absence of atypical features. Treatment should include control of glucose, cholesterol, and triglycerides integrated with exercise and diet for weight loss. Both exercise and weight loss have been shown to improve symptoms in multiple small studies. Regularly evaluating pain and initiating medications such as serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, gabapentinoids, or sodium channel blockers to reduce pain help improve quality of life.

diagnostic tests for the diagnosis of DSPN (receiver operating characteristic curve areas under the curve: 0.76 to 0.90 and 0.75 to 0.82 for electrodiagnostic testing and intraepidermal nerve fiber density, respectively).[14] However, cutoffs for an abnormal test often vary among centers, and patients may be reluctant to complete these tests because of concerns regarding discomfort, particularly for intraepidermal nerve fiber density, which is an invasive test. Additional testing should be considered in patients who present with symptoms that are atypical for DSPN, including asymmetry, non–length-dependent symptoms, motor predominance, acute or subacute onset, and predominant autonomic involvement.[4]

Management

Management of diabetic DSPN is focused both on pain management and risk factor modification to reduce the likelihood of disease progression. Among patients with type 1 diabetes, glycemic control has been shown to prevent the development of DSPN and improve electrodiagnostic and vibratory threshold testing results among individuals with existing DSPN.[15] Although glycemic control likely plays a role in the management of DSPN progression among those with type 2 diabetes, in isolation it has not led to a significant reduction in DSPN incidence.[15] Instead, glycemic control in conjunction with modifying other metabolic syndrome components has shown promise. Weight loss through dietary modification improves multiple metabolic syndrome components among individuals with diabetes as well as neuropathy symptoms.[16] Although weight loss through dietary modification does not significantly improve neurologic examination findings, it has been associated with stabilization of intraepidermal nerve fiber density.[17] Therefore, weight loss through dietary modification may limit DSPN progression. Similarly, exercise is also associated with improvement in patient-reported symptoms and small fiber branching on intraepidermal nerve fiber density, although participants did not have a significant reduction in weight.[18] To date, no intervention has resulted in improvement in electrodiagnostic testing or clinical examination. Thus, multiple interventions, or earlier intervention, may be necessary to modify DSPN progression.

In the absence of disease-modifying therapies, DSPN management is largely focused on pain management. Among individuals with DSPN, pain is often underreported and therefore undertreated.[19,20] American Academy of Neurology (AAN) guidelines from 2022 support the use of four different drug classes for the treatment of painful DSPN: gabapentinoids, which includes gabapentin and pregabalin; serotonin norepinephrine reuptake inhibitors (SNRIs), which includes duloxetine and venlafaxine; tricyclic antidepressants, namely amitriptyline; and sodium channel blockers, such as oxcarbazepine and lamotrigine.[21] Topical medications, such as capsaicin, are also available and are effective in some patients.[21] OPTION-DM (Optimal Pathway for Treating Neuropathic Pain in Diabetes Mellitus), a recent multicenter, randomized, double-blind crossover trial, showed similar clinical efficacy of amitriptyline, duloxetine, pregabalin, and gabapentin among participants with diabetic DSPN.[22] Therefore, the selection of initial treatment for painful DSPN should focus primarily on potential adverse effects and comorbid medical conditions, as well as medication cost. Opioids, including tramadol, likely have no role in the management of painful DSPN given the profound downsides of this class of medication.[21] OPTION-DM also showed that the addition of a second agent

improved pain control among participants with a mean daily pain numerical rating scale of more than 3 (deemed to be nonresponders to monotherapy) after 6 weeks.[22] Therefore, combination therapy is likely a good approach for patients who are refractory to the first pain medication attempted. Setting reasonable expectations and performing regular assessment of a patient's level of pain are important to facilitate medication titration.

Data regarding the impact of nonpharmacologic interventions on painful DSPN are limited. Based on limited evidence, cognitive behavioral therapy, mindfulness, and aerobic exercise may be promising among individuals with DSPN.[23] Although surgical interventions are available, great caution must be used when interpreting the results of a recent randomized trial of spinal cord stimulation in 216 participants because it was an open-label study without a sham surgery in the control arm.[24] Additional investigation into nonpharmacologic pain management approaches for patients with diabetic DSPN is much needed to improve patients' quality of life.

CARDIOVASCULAR AUTONOMIC NEUROPATHY OF DIABETES

Cardiovascular autonomic neuropathy is one of many forms of autonomic dysfunction that occurs in patients with diabetes. Other signs of autonomic dysfunction include gastroparesis, constipation, bladder dysfunction, and sexual and sudomotor dysfunction. This article focuses on cardiovascular autonomic dysfunction as it is associated with increased cardiovascular events, including arrhythmia, myocardial ischemia, and mortality from cardiovascular events as well as all causes. A 2021 meta-analysis of 19 studies (16,099 patients with diabetes) found a pooled relative risk of 3.17 (95% confidence interval, 2.11 to 4.78) for increased all-cause mortality among patients with cardiovascular autonomic neuropathy.[25] Patients may not notice the symptoms of cardiovascular autonomic neuropathy for several years, and late diagnosis increases the risk of mortality.[1] Further, cardiovascular autonomic neuropathy is associated with the development of other diabetes complications such as stroke and renal failure.[26,27] Therefore, identifying patients with cardiovascular autonomic neuropathy is essential to improve outcomes.

Cardiovascular autonomic neuropathy affects both sympathetic and parasympathetic nerves. Like DSPN, cardiovascular autonomic neuropathy follows a length-dependent pattern, affecting the longest autonomic nerves first. As a result, early signs of cardiovascular autonomic neuropathy are from parasympathetic dysfunction of the vagal nerve and include elevated resting heart rate and impaired heart rate variability. These signs are often asymptomatic. Later in the course of the disease, decreased sympathetic activity, namely to peripheral efferent sympathetic vasomotor nerves, leads to decreased peripheral vasoconstriction. Combined parasympathetic and sympathetic autonomic nerve damage eventually leads to decreased cardiac output. Therefore, patients with cardiovascular autonomic neuropathy often endorse dizziness and decreased exercise tolerance early, whereas orthostatic hypotension (defined as a drop in systolic blood pressure of >20 mm Hg or diastolic blood pressure of >10 mm Hg when going from lying to sitting or sitting to standing after 3 minutes) and syncope occur later (CASE 5-2).[28] Increased mortality among patients with cardiovascular autonomic neuropathy is thought to be the result of QT interval prolongation leading to arrhythmias, reduced awareness of myocardial ischemia, and diminished

KEY POINTS

- Electrodiagnostic testing is generally not recommended to confirm clinically diagnosed diabetic distal symmetric polyneuropathy unless the patient has features that are atypical, such as rapid onset, non–length-dependent symptoms, asymmetry, or motor-predominant symptoms.

- Although glycemic control alone prevents the development of distal symmetric polyneuropathy among people with type 1 diabetes, it is insufficient in isolation among people with type 2 diabetes. Therefore, multiple interventions targeting metabolic syndrome components are necessary. Exercise has been associated with improvement in patient-reported symptoms.

- Distal symmetric polyneuropathy management is focused on risk factor reduction and pain management. The American Academy of Neurology guidelines recommend four classes of medications for neuropathic pain management.

- Opioids are not recommended for the treatment of painful diabetic distal symmetric polyneuropathy because limited data support their long-term effectiveness and the emerging downsides include death, overdose, abuse, and addiction.

- Setting reasonable expectations and performing regular assessment of a patient's pain level are essential to titrating medications for neuropathic pain control.

hemodynamic response in the setting of physiologic stressors such as infection or ischemia.

The primary risk factor for developing cardiovascular autonomic neuropathy is prolonged hyperglycemia, which includes both poor glucose control as measured by hemoglobin A_{1C}, as well as diabetes duration.[28] In the population-based Rochester Diabetic Neuropathy Study, autonomic impairment was present in 54% of people with type 1 diabetes and 73% of those with type 2 diabetes.[29] Decreased heart rate variability has also been reported in up to 38% of individuals with prediabetes, suggesting that even low levels of hyperglycemia can result in damage to autonomic nerves.[30] In

CASE 5-2

A 60-year-old man presented to the emergency department after a syncopal episode while watching a July 4th parade. His evaluation after the episode was unremarkable. Although this was the first time that he had lost consciousness, he noted that for the past few years, he had been increasingly "woozy" when getting out of bed to use the bathroom at night. In addition to long-standing diet-controlled type 2 diabetes, he was taking lisinopril for hypertension and atorvastatin for hyperlipidemia.

His neurologic examination was generally unremarkable except for decreased sensation to pinprick on his feet. He underwent testing for cardiovascular autonomic neuropathy in the office, including the Ewing battery; FIGURE 5-1 shows some of his test results. His resting heart rate was 105 beats/min, and his blood pressure while lying down was 120/75 mm Hg and 90/50 mm Hg after standing for 3 minutes. Based on his clinical presentation and test results, he was diagnosed with cardiovascular autonomic neuropathy of diabetes.

COMMENT

Cardiovascular autonomic neuropathy in patients with type 2 diabetes is often asymptomatic in its early stages, and symptoms will only develop late in the course of the disease. FIGURE 5-1 displays the R-R interval during deep breathing for the patient and a normal study for comparison. The R-R interval is a measure of the time elapsed between two successive R waves of the QRS signal on the ECG. Heart rate increases with inspiration and decreases with expiration. Therefore, a graph of the R-R interval versus time would be expected to take a sinusoidal shape that mirrors the pattern of breathing. The patient had an abnormal resting heart rate, orthostatic hypotension, and a blunted heart rate response to deep breathing. Combined, these findings supported a diagnosis of definite cardiovascular autonomic neuropathy. Management should consist of working with his primary care provider to stop medications such as lisinopril that could be contributing to his symptoms, treating risk factors including his diabetes, and anticipatory guidance. Given that his syncopal episode occurred in July, recommending caution and avoidance of standing for prolonged periods in the heat is warranted. Nonpharmacologic and pharmacologic interventions should be considered to improve his blood pressure when standing.

addition, among individuals with type 2 diabetes, traditional cardiovascular risk factors such as age, hypertension, dyslipidemia, and central obesity are also associated with cardiovascular autonomic neuropathy.[31] Therefore, addressing these risk factors, in conjunction with addressing hyperglycemia, is important among people with diabetes to prevent autonomic nervous system damage.[13]

Diagnosis

The American Diabetes Association recommends screening all patients with existing microvascular complications of diabetes (ie, DSPN, retinopathy, or

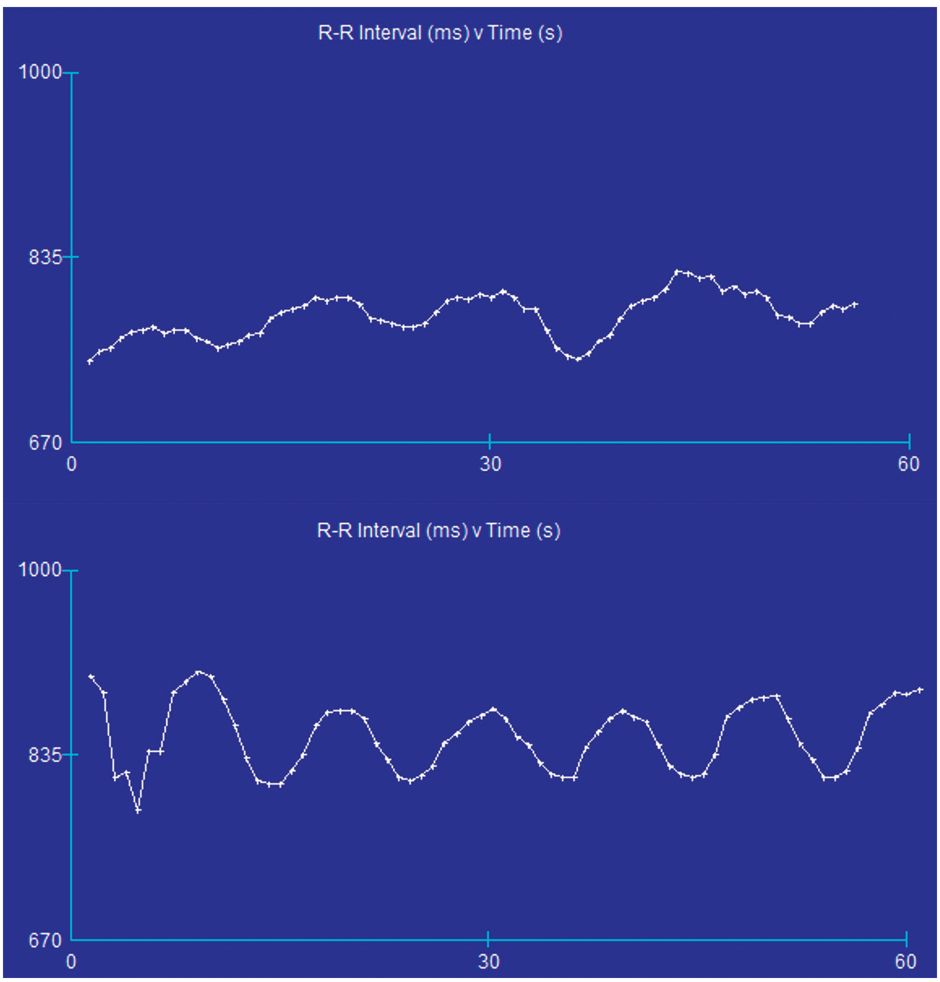

FIGURE 5-1

Graphs depicting heart rate responses to deep breathing. The heart rate of the patient in CASE 5-2 (*A*) compared with a normal study (*B*). This test is an assessment of parasympathetic cardiovagal function. The heart rate increases at the end of inspiration and decreases at the end of expiration. The R-R interval is the distance in milliseconds between successive QRS complexes on a single-lead ECG tracing. A graph of the R-R interval versus time should have a clear sinusoidal shape that mimics the patient's respiratory rate, as seen in *panel B*, when parasympathetic cardiovagal function is intact. This response is blunted in the patient from CASE 5-2, as seen in *panel A*.

KEY POINTS

- Screening for cardiovascular autonomic neuropathy in patients with diabetes is critical since those with cardiovascular autonomic neuropathy are more than two times more likely to die than those without cardiovascular autonomic neuropathy.

- Symptoms of cardiovascular autonomic neuropathy often present late in the disorder with dizziness, orthostatic hypotension, and syncope.

- Risk factors for developing cardiovascular autonomic neuropathy include prolonged hyperglycemia but also include traditional cardiovascular risk factors such as age, hypertension, dyslipidemia, and central obesity.

- Patients with a history of microvascular complications of diabetes, such as distal symmetric polyneuropathy, should be screened for signs and symptoms of cardiovascular autonomic neuropathy. The Ewing battery can often be completed in the office with an ECG and blood pressure cuff.

nephropathy) for signs and symptoms of cardiovascular autonomic neuropathy.[13] As symptoms of cardiovascular autonomic neuropathy often occur late in the course of the disease, proactive screening for signs, namely elevated resting heart rate and orthostatic hypotension, is recommended via a battery of cardiovascular reflex tests.[13] Originally proposed by Ewing and colleagues,[32] these five noninvasive tests include heart rate response to the Valsalva maneuver, standing up, and deep breathing to assess parasympathetic function, and blood pressure response to standing up and sustained handgrip to assess sympathetic function (FIGURE 5-1 in CASE 5-2). The Ewing battery is considered the consensus best test for cardiovascular autonomic neuropathy diagnosis and facilitates disease staging. Individuals with one positive test result on the Ewing battery are considered to have possible or early cardiovascular autonomic neuropathy; two abnormal results reflect definite cardiovascular autonomic neuropathy, whereas the presence of orthostatic hypotension denotes severe cardiovascular autonomic neuropathy.[33] Given the large number of people with diabetes worldwide, concerns exist about the cost and time required to conduct all the tests in the Ewing battery.[13] Therefore, attempts to reduce the number of tests necessary to screen for cardiovascular autonomic neuropathy are ongoing. Although questionnaires have been developed to screen patients for symptoms of cardiovascular autonomic neuropathy, these have not been widely integrated into clinical care.

Management

Treatment of cardiovascular autonomic neuropathy requires a multifaceted approach to reducing risk factors to prevent disease progression while also addressing symptoms. Lifestyle modification to improve glucose control and reduce insulin resistance is essential. The Diabetes Control and Complications Trial and its follow-up observational Epidemiology of Diabetes Interventions and Complications study showed that intensive insulin therapy targeting normoglycemia among 1441 people with type 1 diabetes reduced the incidence of cardiovascular autonomic neuropathy by 45%.[34] Among people with type 2 diabetes, targeting hyperglycemia alone may not be enough; interventions targeting multiple risk factors including hyperglycemia, hypertension, and dyslipidemia may be more effective in this patient population.[35] Surgical weight loss has also been shown to stabilize, but not reverse, cardiovascular autonomic neuropathy progression.[36]

Among patients with orthostatic hypotension, symptomatic management should also be considered. Treatment of orthostatic hypotension is often challenging and includes nonpharmacologic and pharmacologic interventions. Medication lists should be carefully reviewed, and medications that may contribute to hypotension should be discontinued in conjunction with the patient's primary provider. Nonpharmacologic interventions for orthostatic hypotension include (TABLE 5-1) increasing intravascular volume with liberal fluid and salt intake, compression stockings to reduce vascular pooling in the legs, avoiding activities that contribute to vascular dilation such as warm baths, and behavioral modifications such as making changes to posture slowly to reduce symptoms. Pharmacologic interventions include medications such as fludrocortisone, midodrine, pyridostigmine, and droxidopa. TABLE 5-2 lists the typical medication doses and adverse effects.

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

Also known as diabetic amyotrophy or Bruns-Garland syndrome, diabetic lumbosacral radiculoplexus neuropathy occurs most commonly in individuals with type 2 diabetes. It is uncommon, with a prevalence of 2.79 cases per 100,000 people over 5 years in Olmsted County, Minnesota.[37] Although rare, diabetic lumbosacral radiculoplexus may be more common than other inflammatory neuropathies such as Guillain-Barré syndrome, cervical radiculoplexus neuropathy (neuralgic amyotrophy or Parsonage-Turner Syndrome), or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[37] Unlike other diabetic neuropathies, patients who experience lumbosacral radiculoplexus neuropathy often have fairly well-controlled diabetes, with a median hemoglobin A_{1C} of 7.5% in one study.[38] Although the etiology of diabetic lumbosacral radiculoplexus neuropathy is unknown, it often occurs in the setting of recent weight loss, typically more than 4.5 kg (10 lb).[38] No other predictors have been identified; however, a 2022 study of patients with lumbosacral radiculoplexus neuropathy and age- and sex-matched controls suggest that, in addition to diabetes, risk factors for lumbosacral radiculoplexus neuropathy may include a prior history of stroke, elevated body mass index, or a comorbid autoimmune disorder, such as thyroiditis, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or psoriasis.[39]

Patients diagnosed with diabetic lumbosacral radiculoplexus neuropathy endorse acute, severe pain in the hip or thigh described as burning, tightness, or allodynia. They are often able to name the exact day that their symptoms began. This is followed by lower limb weakness that is initially focal and then generalizes to the entire limb. Weakness can progress over months. Pain often improves first so that, depending on how long it takes to seek care, patients may only have asymmetric lower limb weakness, muscle atrophy, and absent knee and ankle

Nonpharmacologic Interventions for Orthostatic Hypotension — TABLE 5-1

In conjunction with a patient's primary care provider, review the existing medication list and discontinue medications that may be contributing to hypotension; offending agents may include antihypertensive medications, antidepressants, and dopaminergic medications for Parkinson disease

Increase intravascular volume

- Increase fluid intake (up to 1.5-3 L/d)
- Liberalize salt intake (up to 6-10 g/d of sodium)
- Waist-high compression stockings to reduce vascular pooling, increase venous return, and increase blood pressure (at least 15-20 mm Hg pressure), although the effect may be limited because of pooling in the splanchnic vasculature

Modify behavior

- Arise slowly, particularly in the morning when orthostatic tolerance is the lowest
- Elevate the head of the bed 30 to 45 degrees to avoid supine hypertension and nocturnal diuresis
- Avoid triggers: eg, Valsalva-like maneuvers, overheating, large carbohydrate-rich meals
- Continue a modified exercise regimen since deconditioning can worsen orthostatic hypotension; focus on recumbent activities

reflexes at the time of evaluation. Sensory loss is not typically seen on examination, although patients may have a concomitant distal symmetric polyneuropathy due to their diabetes.

Significant morbidity occurs with diabetic lumbosacral radiculoplexus neuropathy. The initial pain can be debilitating, and patients often require adaptive devices, such as wheelchairs or walkers for ambulation. Over time, most patients report improvements in pain and strength, although recovery often requires up to 2 years, and few return to normal. Although this is often a unilateral, monophasic acute neuropathy, patients may have a subsequent episode on the opposite leg.[38] Cervical radiculoplexus neuropathy and thoracic radiculopathy are separate entities that can also occur concomitantly with lumbosacral radiculoplexus neuropathy or independently and have a similar presentation and natural history.[40,41] Focal microvasculitis of individual nerves is likely the underlying mechanism for diabetic lumbosacral radiculoplexus neuropathy.

Diagnosis

Because of the severity of symptoms, most patients with diabetic lumbosacral radiculoplexus neuropathy seek care. Diagnosis is largely based on clinical history and examination. Laboratory studies are generally normal; however, biopsy of an involved nerve can show focal or multifocal nerve fiber loss, perivascular mononuclear inflammation and neovascularization in the epineurium, segmental demyelination, and axonal degeneration.[38] CSF studies performed on patients with diabetic lumbosacral radiculoplexus neuropathy are notable for elevated protein, which supports nerve root involvement in

TABLE 5-2 Pharmacologic Interventions for Orthostatic Hypotension

Medication and mechanism of action	Dosing	Potential adverse effects
Fludrocortisone Synthetic mineralocorticoid, expands volume by increasing sodium and water reabsorption	0.1-0.2 mg/d administrated as 1 or 2 doses; start with 0.05 mg/d	Hypokalemia, supine hypertension, peripheral edema, renal failure; use cautiously in patients with congestive failure
Midodrine Direct α_1-adrenergic receptor agonist	2.5-10 mg 3 times a day administered every 3-4 hours during daytime hours	Severe supine hypertension, piloerection, urinary retention; do not use within 4 hours of bedtime; use cautiously in patients with congestive heart failure and chronic renal failure
Droxidopa Synthetic norepinephrine precursor	100-600 mg, 3 times a day, the last dose needs to be administered at least 3 hours before sleep	Headache, supine hypertension, nausea, fatigue; use cautiously in patients with congestive heart failure and chronic renal failure
Pyridostigmine Acetylcholinesterase inhibitor	Start with a 30-mg test dose; if well tolerated, increase to 60 mg, can be administered up to 3 times daily; rarely use more than 120 mg per dose	Wheezing, abdominal pain, diarrhea, hyperhidrosis

this disorder. Nerve conduction studies will often show low-amplitude or absent compound muscle action potentials (CMAPs) in the tibial and peroneal nerves as well as low-amplitude or absent sensory nerve action potentials (SNAPs) in the sural nerve. Asymmetry in nerve conduction studies is usually seen between the affected and unaffected lower limbs. Needle examination will show widespread increased insertional activity, fibrillation potentials, and reduced recruitment of large motor unit potentials. The electrodiagnostic findings are often patchy and cannot be localized to one nerve or root in the affected limb (FIGURE 5-2). Often milder, subclinical electrodiagnostic abnormalities in the contralateral limb are present. MRI of the lower spine is generally unrevealing in these patients; however, magnetic resonance neurography (MRN) may reveal abnormalities. On MRN, signals for fat and blood are suppressed on T2 images so that the nerve appears brighter than the surrounding tissue.[42,43] This approach can be used to examine single nerves or the plexus, although it may not be available at all imaging centers. MRI of the plexus will often show increased

Nerve Conductions

Nerve: Stimulate	Record	Amplitude (mV or μV) R	Amplitude (mV or μV) L	Latency (ms) R	Latency (ms) L	Conduction velocity (m/sec) R	Conduction velocity (m/sec) L
Sural Sensory							
Calf	Ankle	5.3	NR	4.2		40.0	
Reference for age		*≥6.0*	*≥6.0*	*≤4.4*	*≤4.4*	*≥40*	*≥40*
Peroneal Motor							
Ankle	EDB	3.5	1.6	4.5	5.2	42.9	35.9
Below Knee	EDB	3.0	1.3	11.5	13.2		37.0
Above Knee	EDB		1.3		15.9		
Reference for age		*≥2.0*	*≥2.0*	*≤6.5*	*≤6.5*	*≥44*	*≥44*
Tibial Motor							
Ankle	Abd Hal	6.1	2.1	5.7	6.0	40	39
Popliteal fossa	Abd Hal	5.4	1.7	12.6	12.4		
Reference for age		*≥4.0*	*≥4.0*	*≤5.8*	*≤5.8*	*≥41*	*≥41*

Temperatures: L-Calf= 32.1C R-Calf=33.3C

Electromyography

Muscle	Insertional/Spontaneous: Ins	Pwave	Fib	Fasic	Voluntary Motor Unit Potentials: Effort	Recrt	Amp	Dur	Poly
L-Anterior Tibialis	N	0	0	0	N	D1+	+1	+1	+1
L- Medial Gastrocnemius	I	Sust	2+	0	N	D1+	+1	+1	+1
L-Vastus Medialis	I	Sust	2+	0	N	D2+	+1	+1	+1
L-Adductor Longus	I	Sust	3+	0	N	D2+	+1	+1	+1
L-Iliopsoas	I	Sust	4+	0	N	D1+	+1	+1	+1
L- Lumbar paraspinals	I	Sust	1+	0	N	N	N	N	N
R- Medial Gastrocnemius	N	0	0	0	N	N	N	N	N

FIGURE 5-2

Electrodiagnostic studies in a patient with diabetic lumbosacral radiculoplexus neuropathy. These studies were performed 2 months after symptom onset and show decreased compound muscle action potential (CMAP) amplitudes in the left tibial and peroneal motor nerves as well as an absent sural sensory nerve action potential. Fibrillation potentials in muscles are shown in the left lower limb with reduced numbers of voluntary motor unit action potentials in muscles innervated by the peroneal, tibial, obturator, and femoral nerves. There is asymmetry between the sides. These findings are typical for diabetic lumbosacral radiculoplexus neuropathy.

Abd Hal = abductor hallucis; Amp = amplitude; D1+ = decreased by 1; D2+ = decreased by 2; Dur = duration; EDB = extensor digitorum brevis; Fasic = fasciculation potentials; Fib = fibrillation potentials; I = increased; Ins = insertional activity; L = left; N = normal; NR = no response; Poly = polyphasia; Pwave = positive sharp wave; R = right; Recrt = recruitment; Sust = sustained.

KEY POINTS

- **Among people with type 2 diabetes, targeting traditional cardiovascular risk factors as well as hyperglycemia is essential to reduce the incidence of cardiovascular autonomic neuropathy.**
- **Symptomatic management of cardiovascular autonomic neuropathy, particularly among patients with orthostatic hypotension, is critical. A multifaceted approach that includes stopping offending medications, increasing fluid and salt intake, and behavioral modifications is most effective.**
- **Patients with lumbosacral radiculoplexus neuropathy endorse sudden-onset pain in the hip or thigh followed by focal lower limb weakness that worsens over time. Symptoms slowly improve but can take up to 2 years to plateau, and few patients report returning to their prior neurologic baseline.**
- **Nerve conduction studies in a patient with diabetic lumbosacral radiculoplexus neuropathy will show low-amplitude compound muscle action potentials and sensory nerve action potentials as well as fibrillation potentials in muscles in a patchy pattern that does not localize to one nerve or nerve root. Findings will be asymmetric between lower limbs.**
- **There are currently no effective disease-modifying treatments for diabetic lumbosacral radiculoplexus neuropathy, and management is focused on pain management and adaptive devices to improve quality of life.**

T2 signal intensity and thickening of nerves (FIGURE 5-3).[44] It can also be used to assess the terminal branches of nerves for individual muscle involvement. Edema, atrophy, and, in late stages, fatty infiltration can be seen in involved muscles.[45] At this time, neither electrodiagnostic studies nor MRN is used to guide treatment, but they are able to confirm localization and shed light on the extent of nerve involvement, which may inform discussions with patients and their families. If a patient presents to clinical care early in the disease course before improvement in weakness, MRI of the lumbosacral plexus is needed to evaluate for other causes of a radiculoplexus neuropathy such as cancer and other infiltrative conditions.

Management

Currently, no treatment has proven effective for diabetic lumbosacral radiculoplexus neuropathy. Although microvascular inflammation likely plays a substantial role, limited data exist to support the use of immunotherapy in diabetic lumbosacral radiculoplexus neuropathy.[46] A multicenter, double-blind clinical trial of IV methylprednisolone showed no significant difference in functional outcomes between steroids and placebo, although the authors reported that delayed timing of treatment initiation may have played a role.[47] Pain was improved in those receiving steroids; therefore, IV steroids may be indicated early in the course if patients have refractory pain. Earlier diagnosis, which often requires referral to a neurologist, may facilitate better treatment of diabetic lumbosacral radiculoplexus neuropathy as well as improved long-term outcomes. However, the use of steroids in patients with diabetes requires careful care coordination with the patient's primary provider or endocrinologist. Therefore, until effective treatments are identified, management should focus on pain control and providing adaptive devices, such as wheelchairs or ankle-foot orthoses, as needed, to improve mobility.

TREATMENT-INDUCED NEUROPATHY OF DIABETES

Treatment-induced neuropathy of diabetes develops acutely in patients who have rapid improvement in glycemic control after a period of prolonged hyperglycemia. Within 8 weeks of a significant change in hemoglobin A_{1C},

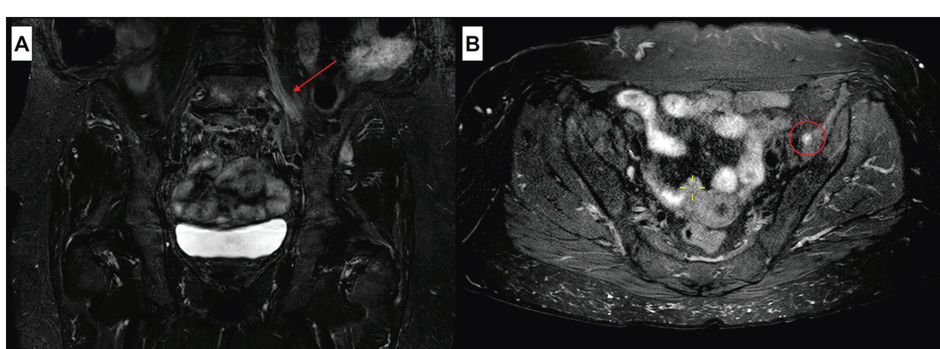

FIGURE 5-3

MRI without contrast of the pelvis in a patient with asymmetric leg weakness. *A*, Asymmetric increased T2 signal and thickening of the left lumbosacral plexus (*arrow*) on a coronal short tau inversion recovery (STIR) image. *B*, Thickening and hyperintensity of the left femoral nerve (*circle*) on the axial fluid-attenuated inversion recovery (FLAIR) image. In the appropriate clinical context, these findings are consistent with a diagnosis of diabetic lumbosacral radiculoplexus neuropathy.

affected patients experience sudden onset of severe, burning, or shocklike pain that can be length dependent or diffuse. Allodynia and hyperalgesia are often present as are autonomic symptoms, including orthostatic hypotension, postprandial fullness, erectile dysfunction, and hyperhidrosis (CASE 5-3).[48] The etiology of this condition is thought to be due to damage to small nerve fibers. Existing theories suggest that the mechanism of disease may be secondary to a relative period of hypoglycemia, leading to inadequate energy production and nerve damage, whereas another theory suggests that a change in glycemic state may lead to an increase in proinflammatory cytokines. Regardless, electrodiagnostic studies in these individuals are often normal, which suggests that large nerve fibers are not involved.

CASE 5-3

A 30-year-old man presented to the electrodiagnostic laboratory for a workup of diffuse, shocklike pain. He had been diagnosed with type 1 diabetes as a teenager and historically had poor glycemic control. However, he noted that he recently got engaged and, for the past 3 months, had been seeking regular medical care to "turn over a new leaf." Three weeks before this presentation, he had developed new burning and shocklike pain in his hands, feet, and abdomen. He had no prior symptoms of neuropathy.

At presentation, he was wearing a baggy sweatshirt, sweatpants, and sandals despite the cold weather. On examination, he had normal strength and reflexes. Vibration sensation and proprioception were also normal. He endorsed severe pain to pinprick in his hands and feet. Similarly, he endorsed pain across his abdomen that did not localize to one dermatome.

A review of his recent laboratory testing revealed that his hemoglobin A_{1C} was historically between 14% and 16% but most recently was 9%. His electrodiagnostic studies were normal, and he was diagnosed with treatment-induced neuropathy of diabetes.

COMMENT

Treatment-induced neuropathy of diabetes occurs in patients who are chronically hyperglycemic and then experience a rapid improvement in glycemic control. The severity and extent of symptoms are driven largely by the magnitude and rate of glucose correction. In this case, the patient's severe symptoms were secondary to the very rapid change in his hemoglobin A_{1C} level, which decreased by up to 7% over 3 months. Treatment-induced neuropathy of diabetes best localizes to small nerve fibers, and examination of large fiber modalities is often normal. The next steps should focus on symptoms; glycemic control should be stabilized (ie, no further decreases in hemoglobin A_{1C} until symptoms begin to improve), and pain control should be initiated. The patient should also undergo assessment for retinopathy and nephropathy as these have both been reported in patients with treatment-induced neuropathy of diabetes. The prognosis is quite good if recurrent episodes of abrupt drops in hemoglobin A_{1C} are avoided.

KEY POINTS

- Treatment-induced neuropathy of diabetes should be considered in an individual with diabetes who presents with acute or subacute pain in the setting of a rapid improvement in glycemic control. Symptoms are best localized to the small fiber nerves and present with burning, shocklike pain, allodynia, and hyperalgesia.

- Patients with treatment-induced neuropathy of diabetes should undergo screening for other microvascular complications as they often experience progression of retinopathy and nephropathy that needs to be appropriately monitored.

- Management of treatment-induced neuropathy of diabetes should focus on preventing neuropathy progression by stabilizing labile glycemic control, managing symptoms via neuropathic pain management, and preventing recurrence. Patients should be counseled that symptoms may improve but may not completely resolve.

- Prevention of treatment-induced neuropathy of diabetes by educating primary care providers and endocrinologists is essential to avoid fast drops in hemoglobin A_{1C} as this is a highly morbid neuropathy. Among patients with existing treatment-induced neuropathy, coordination with the patient's primary care provider or endocrinologist is essential to prevent neuropathy progression.

Treatment-induced neuropathy of diabetes is more common than previously thought. In a retrospective chart review of patients presenting for evaluation of possible diabetic neuropathy, 10.9% met the criteria for treatment-induced diabetic neuropathy.[48] The magnitude and rate of hemoglobin A_{1C} change is directly proportional to the likelihood of symptom onset. Gibbons and colleagues[48] found that individuals who have a decrease in hemoglobin A_{1C} of 2% to 3% over 3 months had a 20% absolute risk of developing treatment-induced neuropathy, whereas those with a decrease of more than 4% had an absolute risk of greater than 80%. Individuals with a greater change in hemoglobin A_{1C} were also more likely to report a larger area of body involvement and more severe pain.

Diagnosis

Diagnosis of treatment-induced neuropathy is based on clinical history and a review of the patient's laboratory results. Graphing the results of hemoglobin A_{1C} over many months often reveals the diagnosis without the need for further testing. For patients who have had care from other providers, acquiring past hemoglobin A_{1C} levels is essential. If typical symptoms start within the period of a 2% to 3% drop in hemoglobin A_{1C}, then the diagnosis is clear. If the patient reports autonomic symptoms, formal autonomic function testing could be considered, although this is unlikely to significantly change management. Screening for retinopathy and nephropathy is essential because patients with treatment-induced neuropathy of diabetes often experience progression of other diabetic microvascular complications.

Management

Management of treatment-induced neuropathy is focused on preventing neuropathy progression, managing symptoms, and preventing recurrence. Case reports suggest that patients with treatment-induced neuropathy often improve with stable glucose control. However, patients should be made aware that the neuropathy may not completely resolve. Further, labile glycemic levels may result in symptom progression, and liberalizing blood sugar control is not recommended. To minimize this risk, patient and, if needed, provider education is warranted. Pain management is essential in patients with treatment-induced neuropathy and should be maximized. As in DSPN, neuropathic pain medications include SNRIs, tricyclic antidepressants, gabapentinoids, and sodium channel blockers. Pain levels should be regularly evaluated as two and even three agents may be necessary for pain control in these patients. However, tricyclic antidepressants should be used cautiously as they may worsen orthostatic symptoms. Preventing recurrence is essential as patients with recurrent treatment-induced neuropathy experience escalation of morbidity including worsening sensory symptoms, motor involvement, and retinal and kidney damage.[49]

Even more important than identifying and treating patients with treatment-induced neuropathy is the primary prevention of this condition. Primary care providers and endocrinologists need to be aware of this entity and the predictable harm of fast drops in hemoglobin A_{1C}. Interventions to increase provider awareness, potentially led by neurologists who most frequently encounter this condition, are needed to prevent this underrecognized condition.

CONCLUSION

Diabetes is a burgeoning worldwide epidemic. Neuropathy is common in patients with diabetes and can present subacutely, as in the case of diabetic lumbosacral radiculoplexus neuropathy, or develop insidiously, as in DSPN and cardiovascular autonomic neuropathy. As the global burden of diabetes on worldwide health continues to grow, even uncommon neuropathies will occur more frequently, and clinicians must be adept at identifying these conditions to facilitate earlier intervention. In all cases, a careful history and neurologic examination are essential for diagnosis. Ancillary studies can supplement a neurologic history and examination, particularly if there is concern for an alternative diagnosis. However, these tests may not be necessary for diagnosis in all cases. Unfortunately, disease-modifying treatments for diabetic neuropathies are limited and, as a result, the focus should continue to be neuropathy prevention and symptom management including pain treatment.

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DISCLOSURE

Continued from page 1401

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Infectious Neuropathies

By Aimee K. Boegle, MD, PhD; Pushpa Narayanaswami, MD, FAAN

ABSTRACT

OBJECTIVE: **This article discusses the clinical manifestations and management of infectious peripheral neuropathies.**

LATEST DEVELOPMENTS: **Several infectious etiologies of peripheral neuropathy are well-recognized and their treatments are firmly established. The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with several central and peripheral nervous system manifestations, including peripheral neuropathies. Additionally, some COVID-19 vaccines have been associated with Guillain-Barré syndrome. These disorders are an active area of surveillance and research. Recent evidence-based guidelines have provided updated recommendations for the diagnosis and treatment of Lyme disease.**

ESSENTIAL POINTS: **Infectious agents of many types (primarily bacteria and viruses) can affect the peripheral nerves, resulting in various clinical syndromes such as mononeuropathy or mononeuropathy multiplex, distal symmetric polyneuropathy, radiculopathy, inflammatory demyelinating polyradiculoneuropathy, and motor neuronopathy. Knowledge of these infections and the spectrum of peripheral nervous system disorders associated with them is essential because many have curative treatments. Furthermore, understanding the neuropathic presentations of these disorders may assist in diagnosing the underlying infection.**

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Address correspondence to Dr Pushpa Narayanaswami, Neurology TCC-8, 330 Brookline Ave, Boston, MA 02215, pnarayan@bidmc.harvard.edu.

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Dr Boegle has received publishing royalties from Wolters Kluwer Health N.V. Dr Narayanaswami has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Alexion Pharmaceuticals, Inc, argenx, and Sanofi and for serving as a consultant for Novartis Pharmaceuticals Corporation; in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Janssen Global Services, LLC, and for serving as an editor, associate editor, or editorial advisory
Continued on page 1443

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Boegle and Narayanaswami discuss the unlabeled use of doxycycline, amoxicillin, and cefotaxime for the treatment of Lyme disease and the unlabeled use of gabapentin, lamotrigine, oxcarbazepine, pregabalin, selective norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine), topical anesthetics (eg, capsaicin, lidocaine), and tricyclic antidepressants (eg, amitriptyline, nortriptyline) for the treatment of neuropathic pain.

INTRODUCTION

Infectious agents are infrequent causes of peripheral neuropathies, although some agents such as herpes viruses, *Borrelia burgdorferi*, and human immunodeficiency virus (HIV) are more prevalent than others (TABLE 6-1[1]). Geography also influences the prevalence of specific neuropathy-causing agents, such as the higher prevalence of leprosy in tropical and subtropical regions. Identifying infectious peripheral nerve diseases is essential because appropriate treatment can be curative or at least decrease morbidity. Recognizing the neurologic manifestations of an infectious syndrome can assist in diagnosing the specific infection. The neurologic presentations of infections vary widely, affecting all parts of the neuraxis, and include meningitis, encephalitis, myelopathies, radiculoneuropathies, and various types of peripheral neuropathies. The underlying infection may be acute, chronic, or a reactivation of a latent infection. Pathogens that affect peripheral nerves primarily include bacteria and viruses. Clinical clues to an infectious neuropathy include the onset of recent aseptic meningitis or a flulike illness, underlying infections such as

hepatitis C or HIV, a syndrome of mononeuritis, mononeuritis multiplex, or less commonly, acute or chronic inflammatory demyelinating polyradiculoneuropathy (AIDP or CIDP). Other clues include vesicular eruptions in herpes zoster or a bull's-eye rash in Lyme disease. Infectious neuropathies should be considered in patients from Asia, Africa, or Latin America who present with a peripheral neuropathy, especially when associated with limb deformities. The mechanisms by which infectious agents cause neurologic symptoms are diverse. While primary infection of peripheral nerves is rare, microbial infections can trigger parainfectious or postinfectious inflammatory and immune responses that lead to nerve injury. Molecular mimicry plays a role in some syndromes, such as Guillain-Barré syndrome (GBS) after *Campylobacter jejuni* infection. Host immune status also influences the risk for infectious neuropathies. This article discusses the etiologies, clinical manifestations, diagnostic tests, and treatments of infectious neuropathies, including the recent association of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with various peripheral nerve disorders.

VIRAL INFECTIONS

This section discusses some of the viruses frequently associated with peripheral neuropathies.

Varicella-zoster Virus

Herpesviridae is a family of more than 130 double-stranded DNA viruses, of which at least eight are known to cause human infection: herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus, cytomegalovirus (CMV), and less frequently, human herpesvirus 6, herpesvirus 7, and Kaposi sarcoma–associated herpesvirus. Herpes viruses are ubiquitous. Seroprevalence rates for one or more of these viruses are more than 80% in the general population.[2] These viruses have a characteristic ability to persist in the host for a prolonged duration after the acute infection and can cause recurrent disease through viral reactivation. Many herpes viruses are neurotropic, and HSV-1, HSV-2, and VZV reside in the dorsal root and trigeminal ganglia and establish a long-term latent infection.[3] In the immunocompetent host, recurrent infections are usually restricted to the dermatomal distribution of the ganglia where the virus is reactivated. However, pharmacologically induced and age-related immunocompromised states place patients at risk for disseminated reactivation with potentially serious neurologic consequences.

VZV causes two conditions: the primary infection, varicella (chicken pox), and the reactivation infection, herpes zoster (shingles). The primary infection is a highly contagious disease, mainly affecting children, and characterized by an initial vesicular rash on the chest, back, and face that spreads over the body. Infection usually results in a mild to moderate illness, but complications, including pneumonia, secondary bacterial infections, and meningoencephalitis, can occur. In the peripheral nervous system, varicella has been rarely associated with postinfectious or parainfectious facial palsy and GBS occurring in the days or weeks after the initial illness.[4,5] The incidence of severe primary infection has declined substantially since the United States implemented the universal VZV vaccination in 1995.

Herpes zoster is a common complication of prior VZV infection. Latent viral particles in the dorsal root ganglia reactivate in the setting of weakened

cell–mediated immunity. Risk factors for reactivation include age older than 60 years, underlying HIV infection, treatment with immunosuppressants, organ transplantation, and underlying malignancies, although most reactivations occur in immunocompetent people.[6] Patients present with several days of itching and burning pain in a localized area, followed by the development of maculopapular lesions that extend from proximal to distal, usually confined to one or two adjacent dermatomes (FIGURE 6-1[7]). The maculopapular rash then transforms into painful, pruritic vesicles, which eventually form a crust, with the skin lesions resolving over 2 to 4 weeks. Systemic symptoms such as fever and malaise occur in a small percentage of patients. Ramsay Hunt syndrome is caused by the reactivation of latent infection within the geniculate ganglion, leading to a triad of vesicular eruptions in the ear and external auditory canal, ipsilateral facial neuropathy, and ear pain. Other associated cranial nerve symptoms include vertigo, hearing loss or hyperacusis, tinnitus, and loss of taste.[8] Facial weakness related to herpes zoster tends to be more severe, and patients are less likely to recover completely than those with traditional Bell's palsy.[9] Herpes zoster

TABLE 6-1 **Common Infectious Causes of Peripheral Neuropathies[a]**

Organism	Clinical syndrome	Treatment
Human immunodeficiency virus (HIV)[b]	Distal symmetric polyneuropathy	Neuropathic pain medications[c]
	Antiretroviral toxic neuropathy	Discontinuation of nucleoside reverse transcriptase inhibitors and start of alternative therapy, topical capsaicin and lidocaine cream, neuropathic pain medications
	Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	IV immunoglobulin (IVIg), plasma exchange
	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Immunomodulatory therapies including IVIg, plasma exchange
	Multiple mononeuropathies	Combination antiretroviral therapy, prednisone, IVIg, immunotherapy
	Cranial neuropathies, diffuse infiltrative lymphocytosis syndrome	Corticosteroids and combination antiretroviral therapy
	Cytomegalovirus (CMV) lumbosacral radiculitis	Oral induction: valganciclovir plus foscarnet; IV ganciclovir substituted if oral intake is not possible; maintenance: oral valganciclovir
Hepatitis viruses[b]	Distal sensory or sensorimotor polyneuropathy	Neuropathic pain medications
	AIDP	IVIg, plasma exchange
	CIDP, multiple mononeuropathies, cranial neuropathies, small fiber sensory polyneuropathy	Immunomodulatory therapies including IVIg, plasma exchange, corticosteroids

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ophthalmicus occurs in the setting of viral reactivation in the trigeminal nerves or gasserian ganglion, with skin eruptions affecting the ophthalmic distribution of the trigeminal nerve and the tip of the nose (FIGURE 6-2[10]). Ocular complications such as conjunctivitis, episcleritis, keratitis, and uveitis can lead to permanent loss of vision.[11] Zoster sine herpete is dermatomal pain without the development of a rash, but this entity is controversial.

The most common complication of herpes zoster is postherpetic neuralgia. Postherpetic neuralgia is variably defined as dermatomal pain persisting beyond 30 to 90 days after the appearance of the skin eruptions.[9] The prevalence depends on which definition is used, and about 20% of patients report pain at 3 months.[12] Postherpetic neuralgia is believed to be secondary to nerve injury caused by the acute herpes zoster infection. Risk factors include older age, prodromal pain, severe pain at onset, severe rash, ophthalmic involvement, diabetes, and immunosuppression.[13] Although most patients notice an improvement in pain over time, postherpetic pain can be persistent and disabling in some.

CONTINUED FROM PAGE 1420

Organism	Clinical syndrome	Treatment
Herpes viruses[b] (eg, varicella-zoster virus, herpes simplex virus, and CMV)	Sacral radiculitis, herpes zoster with postherpetic neuralgia, herpes zoster oticus and other cranial neuropathies, AIDP, plexopathies, diffuse axonal peripheral neuropathy	Antiviral medications, neuropathic pain medications; IVIg or plasma exchange for AIDP
Flaviviruses (eg, West Nile and Zika viruses)	AIDP, acute flaccid myelitis	IVIg or plasma exchange for AIDP, supportive care
Rabies virus	Ascending flaccid paralysis	Human rabies immune globulin (postexposure)
Mycobacterium leprae	Mononeuropathy, distal symmetric polyneuropathy, sensory loss in cooler regions of the body	Antibacterial therapy with a dapsone and rifampin for tuberculoid disease; addition of clofazimine for lepromatous disease for 6 to 12 months
Borrelia burgdorferi	Cranial neuropathies, radiculoneuritis, multiple mononeuropathies, brachial neuritis	IV ceftriaxone per Infections Diseases Society of America guidelines
Corynebacterium diphtheria	Polycranial neuropathy, demyelinating sensorimotor polyneuropathy	Supportive care
Clostridium botulinum	Descending paralysis	Early administration of human-derived or equine-derived antitoxin
Tick paralysis	Ascending areflexic weakness	Removal of tick, supportive care

IVIg = IV immunoglobulin
[a] Reprinted with permission from Anand P, et al, Semin Neurol.[1] © 2019 Thieme Medical Publishers.
[b] Treatment with antiviral therapy is advised in addition to additional therapies listed.
[c] Neuropathic pain medications include pregabalin, gabapentin, oxcarbazepine, lamotrigine, tricyclic antidepressants (eg, amitriptyline, nortriptyline), selective norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine), and topical anesthetics (eg, capsaicin, lidocaine).

KEY POINTS

- **Following acute infection, herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus remain dormant in sensory ganglia, with risk of future viral reactivation.**

- **Risk factors for the reactivation of the varicella-zoster virus and the development of zoster include age (>60 years), underlying human immunodeficiency virus (HIV) infection or malignancy, treatment with immunosuppressants, and organ transplantation.**

- **Postherpetic neuralgia is the most common complication of herpes zoster. Risk factors include older age, the intensity of pain at onset, the severity of the rash, involvement of the ophthalmic division of the trigeminal nerve, diabetes, and immunosuppression.**

- **Herpes zoster ophthalmicus is an ophthalmic emergency and can cause permanent visual loss. Urgent ophthalmologic evaluation is recommended.**

FIGURE 6-1
The skin lesions of herpes zoster.
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In rare instances, herpes zoster can cause motor weakness. Research has described oculomotor palsy associated with ophthalmic herpes, facial paralysis associated with trigeminal or cervical root herpes, flaccid weakness of the limbs associated with zoster involving the spinal roots, brachial or lumbosacral plexus, or peripheral nerves, weakness of the abdominal muscles associated with herpes of the thoracic myotomes, and myelopathy associated with cervical or thoracic zoster. Recovery may be complete, although the recovery of facial paralysis may be incomplete and the duration of weakness may be prolonged.[14]

Herpes zoster is typically a clinical diagnosis. Vesicular fluid polymerase chain reaction (PCR) analysis for VZV DNA is helpful when the differential diagnosis includes other dermatologic conditions. The mainstay of treatment for herpes zoster is antiviral therapy. The course of treatment consists of 1 week of oral acyclovir, valacyclovir, or famciclovir, with the goal of decreasing the number of skin lesions and shortening the acute stage.[15] Treatment should start within 72 hours of the appearance of skin lesions. It is unclear if treatment prevents postherpetic neuralgia.[9] IV acyclovir is recommended for patients with disseminated zoster and in patients at high risk for disseminated zoster, that is, those on long-term glucocorticoids or other immunosuppressants, organ transplantation recipients, patients with advanced HIV disease, or those with lymphoproliferative malignancies.[9] Glucocorticoids may be used as adjunct therapy and may shorten the healing time of skin lesions and reduce pain in the acute period, but they do not appear to prevent the development of postherpetic neuralgia.[16] Herpes zoster ophthalmicus is a serious disease that can result in loss of vision;

FIGURE 6-2
Herpes zoster ophthalmicus affecting the trigeminal V1 distribution. This is a serious condition because there is a risk of permanent vision loss. The presence of a vesicle on the tip or side of the nose is termed the *Hutchinson sign* and predicts an 80% likelihood of ocular involvement. This condition is an ophthalmologic emergency.
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ophthalmologic consultation is an urgent need for these patients. Pain-management strategies for both acute pain and postherpetic neuralgia consist of topical (5% lidocaine, 8% capsaicin patch) and systemic (eg, gabapentin, pregabalin, tricyclic antidepressants) treatments.[12]

Herpes Simplex

Like VZV, HSV-1 and HSV-2 are neurotropic viruses, with high seroprevalence rates in the general population.[2] However, unlike VZV, they are much less likely to cause peripheral nerve disease. Both HSV-1 and HSV-2 are spread through mucosal surfaces and establish latent infection in the trigeminal and dorsal root ganglia. HSV infections typically cause orolabial and genital ulcers, although cases of corneal and retinal disease, cranial neuropathies, and radiculopathy have also been attributed to HSV viral infection or reactivation.[17] HSV-2 has a predilection for the lumbosacral roots, causing radiculitis. Symptoms include low back pain, radicular lower extremity pain, genital pain or paresthesia, and in severe cases, urinary retention, constipation, and weakness in the lower extremities. Such symptoms can occur with or without the characteristic vesicular skin lesions that, if present, are clues to the diagnosis.[17] Elsberg syndrome is a self-limiting syndrome of acute lumbosacral radiculitis and myelitis associated with HSV-2 reactivation in the lumbosacral spinal ganglia. Spine MRI may show cord swelling and hyperintensity on T2-weighted images and swelling and contrast enhancement of the dorsal roots with normal ventral roots.[18] Treatment with valacyclovir or acyclovir may hasten recovery. Reactivation of HSV-1 from the geniculate ganglion has been implicated in Bell's palsy.[19] While spinal fluid PCR analysis can confirm the presence of HSV, the virus is rapidly cleared from the CSF, and negative testing does not exclude infection.[20] Antiviral treatment with acyclovir is the recommended treatment for suspected HSV.

Cytomegalovirus

Similar to VZV and HSV, CMV is a pervasive virus with up to 83% seropositivity in the general population.[21] In the immunocompetent host, severe CMV infection is uncommon, and infection may be asymptomatic or cause nonspecific symptoms,[22,23] although CMV infection is a well-known antecedent trigger for GBS in immunocompetent patients.[24] CMV is the second leading infectious antecedent of GBS after *C. jejuni*; the two account for more than 40% of GBS cases.[25,26] More than 50% of patients with CMV-associated GBS have elevated liver enzymes and antibodies to ganglioside GM2. The GBS subtype in these patients is usually demyelinating. CMV-infected fibroblasts express GM2 on their surface, and anti-GM2 antibodies may be seen in more than 50% of patients with CMV infection who do not develop GBS. However, the presence of GM2 antibodies in a patient with GBS is highly specific for post-CMV GBS.[27]

CMV can cause several peripheral nerve syndromes in immunocompromised patients, including mononeuritis multiplex (due to vasculitis of the epineural arteries), cranial neuropathies, radiculitis, brachial plexopathy, GBS, and myelitis.[28-30] Cauda equina syndrome caused by an acute polyradiculopathy affecting the lumbosacral roots is a well-recognized presentation of CMV radiculitis in patients with HIV infection and occurs rarely in other immunocompromised states. This presentation is less common with the increasing use of highly active antiretroviral therapy (HAART). Patients present

KEY POINTS

- Herpes simplex virus type 2 can cause lumbosacral polyradiculitis with or without myelitis. Symptoms include radicular and perineal pain or paresthesia. Severe cases present with motor weakness and sphincter disturbances. Vesicular skin lesions can help determine the diagnosis.

- Cytomegalovirus (CMV) is the second most common infectious antecedent for Guillain-Barré syndrome (GBS) syndrome after *Campylobacter jejuni*. The presence of anti-GM2 antibodies is highly specific for post-CMV GBS.

- CMV infection in immunocompromised individuals can lead to several peripheral nerve syndromes including myelitis, radiculitis, brachial plexopathies, and mononeuritis multiplex.

KEY POINTS

- CMV polymerase chain reaction testing confirms the diagnosis of CMV-related disease and is useful in monitoring response to treatment.
- HIV is commonly associated with peripheral nerve disorders caused by the direct effect of the virus, other opportunistic diseases, or side effects from antiretroviral medications.
- The most common peripheral nerve disorder in HIV is painful, distal symmetric polyneuropathy.
- Nucleoside reverse transcriptase inhibitors (didanosine, stavudine, and zalcitabine), can cause antiretroviral toxic neuropathy. When possible, affected patients should attempt to transition to alternative antiretroviral therapies.
- In HIV-positive patients with painful sensory polyneuropathy, it is important to exclude alternative or additional etiologies such as diabetes mellitus, vitamin B_{12} and other nutritional deficiencies, concomitant drugs such as isoniazid, and alcohol-related polyneuropathy.

with rapidly progressive bilateral lower extremity weakness, which may be mildly asymmetric. Perineal and perianal numbness may accompany the weakness, and urinary retention and constipation are common. Back pain may be severe. CSF may reveal a polymorphonuclear pleocytosis, which may also be normal or show only mild nonspecific pleocytosis. The detection of CMV by PCR is confirmatory. MRI of the spine may reveal enlargement of the conus medullaris, clumping or enhancement of the lumbosacral nerve roots, or rarely, leptomeningeal enhancement. Nerve conduction studies demonstrate an axonal process with low-amplitude compound muscle action potentials and denervation on EMG; sural sensory nerve action potentials may also be low-amplitude or absent in some patients. Pathology reveals focal necrosis of the roots and subpial regions of the conus medullaris and lumbar spinal cord in addition to inflammatory infiltration with neutrophils, plasma cells, lymphocytes, and macrophages. CMV inclusions may be seen in Schwann cells.

In addition to confirming the diagnosis, CMV PCR testing assists in monitoring response to treatment. Treatment results in varying degrees of clinical improvement, but residual deficits are common.[31,32] Oral valganciclovir, which has better bioavailability than oral ganciclovir, is the recommended treatment, usually in combination with foscarnet, for induction treatment of severe disease because dual treatment has been associated with better outcomes.[33] If oral intake is not possible, IV ganciclovir is substituted for oral valganciclovir. Patients continue treatment until they have symptomatic improvement, at which time long-term maintenance oral monotherapy with valganciclovir is continued. Monotherapy with either agent may be used in milder disease.

Human Immunodeficiency Virus

Most patients with HIV experience some degree of peripheral neuropathy during their illness. HIV-related peripheral nerve disorders can be directly caused by the virus, other opportunistic infections in the setting of immunodeficiency, or antiretroviral medications. The most common peripheral nervous system disorder in HIV is distal sensory polyneuropathy. This occurs in 20% to 60% of patients and affects both small and large sensory fibers, with prominent loss of small unmyelinated fibers (CASE 6-1).[34]

Clinical symptoms of HIV distal sensory polyneuropathy include painful paresthesia and numbness affecting the extremities in a length-dependent distal symmetric distribution. Some patients are asymptomatic, however, and the neuropathy is identified only on examination. Motor symptoms are usually absent. Neuropathic pain is frequent.[35,36] Examination reveals various combinations of length-dependent loss of pain and temperature sensation, reflecting small fiber dysfunction, impaired proprioception, and distal vibratory sensation due to large fiber dysfunction. Ankle reflexes may be absent. Nerve conduction studies reveal a length-dependent sensory neuropathy with axonal features (low-amplitude sensory nerve action potentials with relatively preserved conduction velocities); nerve conduction studies are typically normal in patients with pure small fiber neuropathies.

The pathogenesis of HIV distal sensory polyneuropathy is likely multifactorial. HIV infection of peripheral nerves occurs both with and without clinical neuropathy. HIV infection of dorsal root ganglia cell cultures induces expression of proinflammatory cytokines, which mediate cell death.[37] Neuropathologic

studies reveal a reduction in dorsal root ganglia neurons with inflammatory cell infiltration by lymphocytes and macrophages.[38] Mitochondrial dysfunction and impaired replication due to the effects of the HIV infection and some antiretroviral drugs have been implicated in the pathogenesis of neuropathy.[39] Other proposed factors are neurotoxic mediators secreted by activated macrophages and HIV envelope protein gp120–mediated Schwann cell toxicity.[39-41] Some antiretroviral therapies (ARTs) used in the treatment of HIV, especially the nucleoside reverse transcriptase inhibitors (didanosine, stavudine, and zalcitabine), are known to cause an antiretroviral toxic neuropathy. This entity can be clinically indistinguishable from HIV distal sensory polyneuropathy except for its temporal association with the initiation of antiretroviral therapies within the preceding 6 months, more acute onset of symptoms, and the earlier involvement of the upper extremities.[42] While nucleoside reverse-transcriptase inhibitors are less commonly used in recommended HIV HAART regimens, they are still a key component of treatment in areas with limited resources. Discontinuation of nucleoside reverse transcriptase inhibitors can lead to improvement of antiretroviral toxic neuropathy.[43] Workup of HIV-positive patients presenting with painful sensory neuropathy should include testing for other common causes of neuropathy and comorbid conditions such as diabetes mellitus, vitamin B_{12} deficiency, other nutritional deficiencies, concomitant drugs such as isoniazid used for tuberculosis, and alcohol-related polyneuropathy

CASE 6-1

A 43-year-old man with a 20-year history of well-controlled human immunodeficiency virus (HIV) presented to the neurology clinic for an evaluation of 6 months of painful sensations affecting his bilateral distal lower extremities. He described burning pain and paresthesia in both feet. There was no associated illness or recent infectious exposures. He denied back pain. Other than HIV, his medical history was notable for hypertension. He denied tobacco, alcohol, or drug use. His medications included amlodipine, bictegravir, emtricitabine, and tenofovir alafenamide. The neurologic examination demonstrated normal muscle bulk, tone, and strength. There was hyperalgesia to pinprick in both feet, extending from the toes to the ankles. There was mild loss of vibratory sensation at the toes. Ankle jerks were absent, but all other reflexes were normal. Routine serologic studies (hemoglobin A_{1C}, vitamin B_{12}, methylmalonic acid, and serum immunofixation) were normal. His HIV viral load was undetectable, and his $CD4^+$ count was normal. Symptomatic treatment with gabapentin was started with good control of symptoms.

COMMENT

This patient presented with a painful, predominantly sensory, distal symmetric polyneuropathy. Testing for common causes of neuropathy was negative, and his only risk factor for neuropathy was a long-standing diagnosis of HIV infection. The antiretroviral drugs he was on are not typically associated with peripheral neuropathy. Testing for common etiologies of neuropathy should be part of the workup since they may compound the underlying infectious etiology and are treatable.

should be excluded. Treatment consists of symptomatic management with agents used for neuropathic pain, optimization of comorbidities such as depression and impaired sleep, and judicious withdrawal of neurotoxic agents.[36]

HIV infection is also associated with focal and generalized sensorimotor neuropathies. Cranial neuropathies (commonly facial palsies) and acute inflammatory demyelinating polyneuropathy have been described in the setting of HIV seroconversion.[36,44] Mild lymphocytic pleocytosis in the CSF in comparison to the usual albuminocytologic dissociation in GBS may indicate HIV seroconversion.[44] Immune-mediated mononeuritis multiplex has been reported, although multiple mononeuropathies can occur rarely due to an opportunistic infection with CMV.[45,46] Systemic symptoms such as weight loss and myalgias may accompany vasculitic mononeuritis multiplex. Cryoglobulinemia, either in the setting of HIV infection or due to a coinfection with hepatitis C (see the Hepatitis C Virus section), can also cause mononeuritis multiplex. The presence of HIV-associated vasculitis has declined since the advent of HAART. Other types of neuropathy associated with HIV infection include CIDP, autonomic neuropathies, and neuropathies due to opportunistic infections (eg, CMV polyradiculitis, herpes zoster radiculopathy).[36] Generally, inflammatory neuropathies occur at higher CD4 counts, and neuropathies from opportunistic infections occur at lower CD4 counts.[45,46]

A small percentage of HIV-infected patients develop a hyperimmune response to HIV infection characterized by the expansion of $CD8^+$ lymphocytes. This condition, termed *diffuse infiltrative lymphocytosis syndrome*, is a multisystem disorder characterized by visceral lymphocytic infiltration, presenting with parotiditis and lymphadenopathy, and involves the lungs, liver, kidneys, gastrointestinal tract, and nervous system. Involvement of the salivary gland causes sicca syndrome. Peripheral nerve manifestations of this syndrome include facial nerve palsies, polyradiculopathies, radiculoplexopathies, and sensorimotor polyneuropathy.[36] Nerve biopsy shows perivascular CD8 cell infiltrates without mural necrosis and with abundant HIV protein in macrophages. Treatment aims to control the underlying HIV infection with the initiation of HAART. Corticosteroids may be used as adjuvant therapy to help limit the progression of the syndrome, particularly in patients who have no response to HAART.[36,47]

A rare motor neuron disease syndrome has been described in HIV infection. This disorder is important to recognize as it may respond to the treatment of the HIV infection. Clinically, HIV motor neuron disease is indistinguishable from amyotrophic lateral sclerosis (ALS), except that it can present subacutely and progress rapidly over weeks to months. Patients tend to be younger than traditional cohorts with ALS, but they present with similar symptoms of fasciculations and weakness with or without hyperreflexia.[48-50] Early initiation of antiretroviral therapy has led to the reversal of the motor neuron disease in some patients.[49] Evidence shows that human endogenous retrovirus-K (HER-K) activation by HIV infection can be cytotoxic. HER-K activation causes a syndrome resembling ALS in transgenic mice, and it is postulated that controlling the HIV infection can reduce HER-K activation.[48] HER-K activation and modulation of the immune system has been described in ALS, and the level of antibodies to HER-K appears to correlate with disease severity.[51] A proof-of-concept study to suppress HER-K activity using antiretroviral therapy in patients with sporadic ALS is ongoing.[52]

Hepatitis C Virus

Although the liver is the primary target of the hepatitis C virus, chronic hepatitis C infections due to viral persistence are associated with systemic inflammation and immunologic responses that affect almost every organ system. Nearly 50% of patients with chronic hepatitis C virus infection have an associated neurologic complication.[53]

Peripheral neuropathy develops in about 10% of patients with hepatitis C virus infection. Hepatitis C virus infections can be associated with mixed cryoglobulinemia in up to 50% of patients, which increases the risk of peripheral neuropathy.[54-56] Various types of peripheral neuropathy are associated with hepatitis C virus infection. Most frequently, patients have a painful, distal symmetric sensory or sensorimotor axonal polyneuropathy. Large fiber neuropathy is uncommon. Mononeuropathies, mononeuritis multiplex, and rarely, demyelinating neuropathies have been reported.[54,57,58] Asymptomatic neuropathy has also been identified in patients with untreated hepatitis C virus infections. The cause of hepatitis C virus-related neuropathy remains unclear. While infection is an independent risk factor for the development of neuropathy, one study found that age was an independent predictor of neuropathy, but the duration of hepatitis C virus infection was not.[59] Cryoglobulins are associated with vasculitis and subsequent nerve damage; the direct neurotoxic effect of hepatitis C virus may also be a factor.[55] The activity of cryoglobulins appears to correlate with the type and severity of the neuropathy. Mild cryoglobulinemic vasculitis seems to be associated with small fiber sensory neuropathy, whereas mononeuritis multiplex and sensorimotor neuropathies are associated with active cryoglobulinemia with skin lesions.[56] The underlying pathology in both cryoglobulin-negative and cryoglobulin-positive patients seems to be a vasculitic process.[60] A Cochrane review did not find the high-quality evidence needed to make recommendations for treating hepatitis C virus–related peripheral neuropathies.[61] Immunosuppression with rituximab and concomitant antiviral therapy is recommended in severe vasculitis with renal dysfunction, extensive skin lesions, or mononeuritis multiplex.[62]

Severe Acute Respiratory Syndrome Coronavirus 2

At the time of writing, the World Health Organization (WHO) reports more than 770 million confirmed cases of SARS-CoV-2 globally, with more than 7 million deaths.[63] COVID-19 is caused by SARS-CoV-2, a member of the Coronaviridae virus family, which contains four genera. SARS-CoV-2 belongs to the genus *Betacoronavirus*. Coronaviruses are single-stranded, enveloped RNA viruses named for their crownlike appearance on electron microscopy. The SARS-CoV-2 sequence is similar to other human coronaviruses that are responsible for 15% of all cases of acute viral nasopharyngitis or the common cold.[64]

The clinical features of COVID-19 can range from an asymptomatic infection, to a mildly symptomatic respiratory or gastrointestinal illness, to a severe illness with coagulopathy and systemic multiorgan failure. Symptoms of peripheral nerve involvement were reported in 19 of 214 hospitalized patients (8.9%) with COVID-19 in Wuhan, China.[65] One of the earliest and most frequent peripheral neurologic symptoms is anosmia or distorted smell with or without ageusia or dysgeusia.[65] Dysfunction of taste and smell is now considered a cardinal feature of SARS-CoV-2 infection, with varying worldwide prevalence estimates. In one

KEY POINTS

- HIV seroconversion can be associated with cranial neuropathies (especially affecting the facial nerve) and GBS. Mild lymphocytic pleocytosis differentiates this syndrome from typical GBS.
- Immune status in HIV correlates with the type of peripheral nerve disorder. For patients with HIV, inflammatory neuropathies occur at higher CD4 counts and opportunistic infections at lower CD4 counts.
- Diffuse infiltrative lymphocytosis syndrome is a hyperimmune response to HIV infection characterized by the expansion of $CD8^+$ lymphocytes. Patients present with multisystemic lymphocytic infiltration, which can involve peripheral nerves.
- A motor neuron syndrome resembling amyotrophic lateral sclerosis can occur rarely in HIV-infected patients. This syndrome presents subacutely and progresses more rapidly than amyotrophic lateral sclerosis.
- Mixed cryoglobulinemia is present in up to 50% of patients with hepatitis C and increases the risk of peripheral neuropathy.
- Vasculitis appears to be the underlying pathology in both cryoglobulin-positive and cryoglobulin-negative hepatitis C patients with peripheral neuropathy.

study of patients with COVID-19, olfactory and gustatory symptoms were reported in 86% and 88% of patients, respectively.[66] A systematic review and meta-analysis revealed a geographic variation in the prevalence of chemosensory symptoms, with a higher prevalence in Western countries compared with East Asian countries.[67] Possible reasons for this geographic difference include underreporting symptoms and genetic variations at the level of the virus or the host.[68] Olfactory dysfunction can occur in otherwise asymptomatic patients; it may be the first symptom of the illness and is typically abrupt in onset, and it may persist after recovery from the acute illness.[66,69] In many cases, however, the chemosensory dysfunction is short lasting, with recovery or significant improvement from a few days to 2 weeks.[68] One study of 97 patients showed that approximately 45% of patients reported full recovery of olfaction, 53% of patients reported partial recovery, and 2% of patients reported no recovery over a period of 4 to 12 months.[69] The pathophysiology of olfactory and gustatory dysfunction in COVID-19 is not fully understood.

Several other peripheral nerve disorders have been described in association with COVID-19, most frequently GBS. However, most of the data are limited to case reports or uncontrolled case series. Therefore, the causal link between these disorders and COVID-19 is difficult to establish, and larger prospective controlled studies are necessary.

Cranial neuropathies have been reported in association with COVID-19 infection. In a systematic review of 36 articles describing 56 patients, cranial neuropathies without further peripheral involvement were noted in 32 patients, while the rest of the patients had cranial neuropathies in the setting of GBS. Neuropathies affecting all cranial nerves except the spinal accessory were noted; the facial, abducens, and oculomotor nerves were most frequently affected.[70]

All variants of GBS, including axonal variants and focal syndromes, have been associated with COVID-19 with an unclear causal relationship. GBS has been reported to be the initial presentation of COVID-19, but the exact prevalence of COVID-19–associated GBS is unknown.[71-74] An epidemiologic study from the United Kingdom found no clear causative link between COVID-19 and GBS. The study attributed a lower incidence of GBS during the pandemic to a decreased risk of other infections due to isolation and masking.[74] Unsurprisingly, critical illness neuropathy and critical illness myopathy have been reported in severely ill patients with COVID-19 cared for in the intensive care unit.[75]

Case reports have described worsening of CIDP after COVID-19, but COVID-19 and a new diagnosis of CIDP do not seem to be associated.[76,77] Neuralgic amyotrophy has been rarely reported, occurring a few weeks after COVID-19.[78,79] Single and multiple mononeuropathies are described in hospitalized patients with severe COVID-19. It is not uncommon to see patients with severe COVID-19, who required mechanical ventilation during the acute illness, presenting in the recovery phase with mononeuropathies. The etiology in these cases may be multifactorial, and prone positioning is associated with the development of mononeuropathies. The neuropathies associated with prone positioning most frequently involve the ulnar, radial, and sciatic nerves and the brachial plexus. They are axonal, and the risk of these neuropathies increases with older age, obesity, and underlying diabetes mellitus.[80,81]

The term *long COVID* applies to postacute sequelae of COVID-19 infection. Peripheral nervous system involvement in long COVID includes persistent

olfactory and gustatory dysfunction; one study reported these symptoms in more than one-quarter of patients.[82] Frequent symptoms of long COVID include fatigue, shortness of breath, exercise intolerance, lightheadedness, hyperhidrosis, burning pain, joint pain, headaches, and brain fog.[83] Patients with fatigue have been reported to have abnormalities on measures of autonomic function compared with patients without fatigue.[84] In one study, the most common finding was orthostatic intolerance without objective findings on testing, and most patients had mild abnormalities on autonomic function testing.[85] Additionally, small fiber neuropathy has been reported in one small series. In a retrospective study of 13 patients with post–COVID-19 painful paresthesia, six patients had evidence of small fiber neuropathy on skin biopsy, and two of those six also demonstrated abnormal autonomic testing.[86] Abnormalities of corneal nerve fibers on confocal microscopy have been reported in patients after COVID-19 compared with controls.[87] Overall, the nature of long COVID and the pathophysiology of the associated neurologic disorders remains uncertain, with limited quantity and quality of evidence.[86]

After COVID-19 vaccination, based on Vaccine Safety Datalink data, the US Centers for Disease Control reports a higher risk of GBS with a viral vector vaccine but no increased risk with mRNA vaccines. Case reports have noted GBS or GBS variants following a recombinant viral vector vaccine. A cohort study using the vaccine safety datalink also found an increased risk of GBS with the Ad26.COV2.S vaccine.[73,88] These data should be interpreted cautiously because the surveillance systems are based on passive reporting, and case reports are subject to bias. This remains an ongoing area of active surveillance.

KEY POINTS

- Olfactory dysfunction in severe acute respiratory syndrome coronavirus 2 infection may occur in otherwise asymptomatic patients and may be the presenting symptom of COVID-19.
- A higher risk of GBS has been reported with the Ad26.COV2.S vaccine but not other COVID-19 vaccines.

Zika Virus

Zika virus is a mosquito-borne flavivirus transmitted by *Aedes* species mosquitoes and through sexual intercourse and blood transfusions. Zika virus has been associated with GBS, with a 2- to 20-fold increase in GBS incidence from baseline during the Zika virus epidemics. Up to 98% of patients with GBS during Zika virus outbreaks had IgM or IgG antibodies to Zika virus compared with 55% of controls. Immune–mediated molecular mimicry is the postulated mechanism. All subtypes of GBS have been described with a mean period of 7 days between infection and GBS onset. Electrophysiologic studies in French Polynesia revealed an acute motor axonal neuropathy (AMAN) while in the Americas, the picture is more of a typical AIDP.[89] Zika has also been rarely associated with acute myelitis, with weakness, sensory, and sphincter involvement with spinal cord hyperintensity and swelling on spine MRI.[90]

Infectious Motor Neuropathies

Several viral infections have a predilection for the anterior horn cells, leading to acquired motor neuronopathies. Among these, poliomyelitis is one of the best characterized. Poliovirus is a highly infectious enterovirus and member of the Picornaviridae family. It is transmitted via fecal-oral contact and respiratory droplets. Although most individuals experience asymptomatic infection, approximately 1% of infected individuals will develop an acute paralytic syndrome. This form of the illness typically manifests as several days of fever, sore throat, and vomiting, followed by meningeal signs (eg, headache, nuchal rigidity, neck and back pain). Painful muscle spasms occur before the development of generalized flaccid weakness, typically spinal, although bulbar

involvement is described. MRI findings may show T2 hyperintensity of the anterior horn of the spinal cord. CSF typically shows a mild to moderate pleocytosis and elevated protein. Treatment is supportive, and recovery from acute illness is typically incomplete, resulting in permanent paresis of the most affected extremities or bulbar muscles. Although vaccination has eradicated wild poliovirus in much of the world, several regions in Africa, Asia, and the Middle East continue to report new cases each year. More recently, cases of live-vaccine–induced polio in nonimmunized individuals have been reported.[91] Vaccination remains the main means of polio prevention. Poliomyelitis is in the differential diagnosis of other acute flaccid motor-predominant syndromes such as GBS in endemic areas. Two major distinguishing features between poliomyelitis and GBS are the pain and the typical asymmetric involvement in poliomyelitis.

Additional viruses have been associated with poliolike paralytic syndromes. In 2014, another member of the Picornaviridae family known as enterovirus D68 caused an outbreak of lower respiratory tract infections in the pediatric population. Amid this and subsequent outbreaks were rare cases of acute flaccid myelitis in children and young adults. These patients presented with a viral prodrome, followed by asymmetric, progressive weakness. MRI findings revealed short segmental T2 hyperintensities affecting the gray matter of the spinal cord, and CSF findings showed mild elevation in cells and protein. IVIg is currently the recommended treatment, but its effectiveness is unclear, and full motor recovery is uncommon.[92] Although the association between acute flaccid myelitis and enterovirus D68 remains, research regarding direct causation and treatment options continues.[93]

The most common neuromuscular manifestation of infection with the mosquito-borne flavivirus, West Nile virus, is an asymmetric poliomyelitis syndrome with or without bulbar and respiratory involvement. West Nile virus can also cause a GBS-like syndrome, myositis, polyradiculitis, or more focal presentations such as brachial plexopathy. Treatment is supportive.[94]

Despite the various viral etiologies, electrodiagnostic studies in acute flaccid myelitis or the poliomyelitis syndromes demonstrate similar findings. Decreased motor unit potential recruitment may be the only finding early on, with progression to decreased amplitude or absent compound muscle action potentials in the paretic limbs. Subsequent EMG findings consist of widespread denervation in corresponding myotomes, followed by reinnervation.

BACTERIAL INFECTIONS

Although bacterial infections causing neuropathies are uncommon, it is important to recognize them because they may have curative treatments.

Leprosy

Leprosy, or Hansen disease, remains a common cause of chronic, severe, mutilating, infectious neuropathy in tropical and subtropical parts of the world. Data from the WHO show more than 140,000 new cases were reported globally in 2021, with cases predominantly occurring in India, Brazil, and Indonesia.[95] The disease remains endemic in Africa, the eastern Pacific, and western Mediterranean regions. Rare cases of leprosy have been reported recently in the United States, mainly central Florida where it may be endemic.[96] Most leprosy infections are due to the gram-positive, acid-fast bacillus *Mycobacterium leprae*. In 2008, *Mycobacterium lepromatosis* was identified as an additional causal agent

of leprosy.[97] Disease transmission occurs through droplets of nasal secretions and skin shedding by close and frequent contact with infected individuals. In the southern United States, some armadillos are naturally infected and human transmission is possible, but the magnitude of risk is unknown and likely low, with higher risk in people who hunt, kill, process, or eat armadillo meat.[98] The incubation period ranges from months to years, and it can be as long as 20 years.[99] Estimates indicate that only 5% of individuals exposed to the bacteria are infected, and only 20% of those develop clinical leprosy.[100] Factors such as genetics, nutritional status, and hygiene may modify the risk of developing the disease.[99,100] Clinical presentations of leprosy are varied, and depend on the genetic susceptibility factors and immune response profiles of the host. The two salient clinical features are skin lesions and neuropathy. Subtypes of leprosy include tuberculoid and lepromatous leprosy. Tuberculoid leprosy represents one end of the spectrum, in which a robust cell-mediated immune response contains the infection, decreases the overall bacterial load, and leads to a few, well-circumscribed, anesthetic skin lesions. These skin lesions have well-defined margins, and *M. leprae* are rarely detected. On the other end of the spectrum is lepromatous leprosy, in which there is a humoral response to infection, a high bacillary load, and more widespread skin, visceral, and nerve manifestations, with multiple, symmetric lesions in the skin, nerves, eyes, and internal organs. An operational, clinical classification of leprosy by the WHO includes paucibacillary and multibacillary leprosy. The WHO characterizes paucibacillary leprosy by one to five skin lesions, a negative skin smear for *M. leprae*, and peripheral nerve involvement that is absent or restricted to one nerve. Multibacillary leprosy consists of more than five skin lesions or a positive skin smear for *M. leprae* at any site irrespective of skin lesions and more than one nerve involvement regardless of the number of skin lesions.[101] Tuberculoid leprosy is paucibacillary and lepromatous leprosy is multibacillary.

Skin lesions are common for the initial presentation of leprosy. Numbness and weakness due to peripheral nerve involvement may accompany skin lesions. Less commonly, a trophic ulcer due to anesthesia of the hand or foot may be the presenting feature. Skin lesions with elevated red margins, an atrophic center, anhidrosis, and loss of hair suggest the tuberculoid form; confluent skin lesions, leonine facies (deeply furrowed and lumpy face), madarosis (loss of eyebrows or eyelashes), and greater neuropathic involvement are seen in the lepromatous form. Skin lesions are hypoesthetic or anesthetic, with a patient's sense of temperature affected first, followed by touch and pain sensations. In endemic areas, a complete skin examination may assist in diagnosing leprosy in patients with unexplained neuropathies. Because the optimal temperature for *M. leprae* growth is 27°C to 30°C (81°F to 86°F), skin lesions tend to appear in the cooler, distal areas of the body, such as the face, earlobes, and extremities. For the same reason, cranial and peripheral nerves at superficial locations, such as the testes and anterior chamber of the eyes, are affected. Leprosy is one of the preventable causes of blindness.[101]

In general, the peripheral neuropathy of leprosy presents with negative symptoms such as hypoesthesia or anesthesia, inability to sweat, painless ulcers, and patchy motor weakness.[101] Positive phenomena such as pain or dysesthesia are uncommon. The neuropathy predominantly affects small fibers in a patchy distribution.[102] Pure motor involvement occurs rarely. Tender, beaded,

KEY POINTS

- **Leprosy remains a common cause of infectious neuropathy in the tropics and subtropics, with the highest incidence occurring in India, Brazil, and Indonesia.**

- **The host immune response determines the clinical presentation of leprosy. A robust cell-mediated response results in paucibacillary tuberculoid leprosy, whereas an ineffective humoral response results in multibacillary lepromatous leprosy.**

- **Classic symptoms of leprous neuropathy include anesthesia, inability to sweat, and patchy motor weakness. Painless skin ulcers may be present. Intraneural inflammation causes nerve thickening.**

thickened nerves are a characteristic sign of leprosy and can affect 40% to 65% of patients in endemic areas. Damage to peripheral nerves results from direct colonization and multiplication in the Schwann cells by *M. leprae*, leading to an inflammatory reaction triggered by T cells and macrophages, with formation of granulomas and eventual demyelination and axonal degeneration.[103] Single nerve thickening suggests symmetric tuberculoid leprosy; multiple nerve enlargements favor lepromatous leprosy. Thickening of nerves affects the ulnar nerves just above the elbow (most commonly), great auricular nerves (**FIGURE 6-3**[101]), dorsal cutaneous branches of the ulnar nerve at the wrist, median and superficial radial nerves, the common peroneal nerve, the superficial peroneal nerve, the posterior tibial nerve, and sural nerves.

FIGURE 6-3
Great auricular nerve enlargement in leprosy can be diagnosed by having the patient look to the side. It is usually easier to see rather than feel.
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Mononeuropathy and mononeuropathy multiplex are the most common presentations of peripheral neuropathy in leprosy, affecting the nerves listed above, and frequently involving the ulnar and common peroneal nerves. A small proportion of patients with lepromatous leprosy can develop a distal symmetric small fiber sensory polyneuropathy.[99] Extensive, confluent mononeuropathies may simulate a polyneuropathy, requiring careful examination. Multibacillary leprosy can be associated with autonomic dysfunction, which is usually focal, accompanying the sensory neuropathy, resulting in dry skin, cracking, and ulceration of the skin.[104] Cranial neuropathies most commonly involve the facial and trigeminal nerves. An additional characteristic of leprosy is patchy cranial neuropathy, involving nerve branches, and it is more common in chronic lepromatous leprosy, causing the leonine facies.[105]

Pure neuritic leprosy, first described in India, is a rare form of leprosy, and it has since been reported in Brazil and Nepal. It presents most commonly as a sensory, less frequently motor, mononeuropathy, more commonly involving the upper extremities in young men. Focal autonomic changes may be seen.[106] It can be difficult to diagnose without skin lesions, and a high index of suspicion is required in patients from endemic areas. A diagnosis requires nerve biopsy.

Leprosy causes long-term sequelae of deformities and disability, so it is important to provide patients with an early diagnosis and treatment. Clinicians in nonendemic areas should consider leprosy in the differential diagnosis of cryptogenic neuropathies, especially in patients from endemic areas. Common deformities include claw hand, foot drop, trophic ulcers, and absorption of the fingers and toes in the late stages. Nerve conduction studies reveal earlier and more extensive abnormalities than the clinical evaluation and frequently show a sensory or sensorimotor axonal mononeuropathy multiplex, which is not specific

for leprosy. MR neurography and nerve ultrasonography (FIGURE 6-4) have been used to provide objective evidence of proximal neuropathies.[101] Slit-skin smears are usually performed first, followed by skin biopsy. Slit-skin smears are usually obtained from six sites (both earlobes, both elbows, and both knees) and also from lesions. To obtain a slit-skin smear, a clinician makes a skin incision 3 to 5 mm long and 2 to 3 mm deep and, before withdrawing the blade, scrapes the inner surface of the wound and transfers the material to a slide to make a small circular smear. The detection of *M. leprae* remains the mainstay of diagnosis. In tuberculoid leprosy, noncaseating granulomas present at diagnosis, while *M. leprae* are rarely seen or are absent. The presence of inflammatory cells in the dermis help to confirm the diagnosis in these cases. A nerve biopsy is performed in pure neuritic leprosy or when the diagnosis remains unclear despite skin biopsy, nerve conduction studies, and imaging (FIGURE 6-5 and FIGURE 6-6[102]).

The clinical presentation dictates the treatment regimen (paucibacillary versus multibacillary). The WHO developed the standard multidrug therapy of dapsone, rifampin, and clofazimine by expert consensus in 1982, and in 2017 they recommended the multidrug therapy regimen that is currently used.[107]

KEY POINT

- **Early diagnosis and treatment are essential to prevent leprosy-related deformities and disability. Clinicians in nonendemic areas should consider leprosy in the differential diagnosis of cryptogenic neuropathies, especially in patients from endemic areas.**

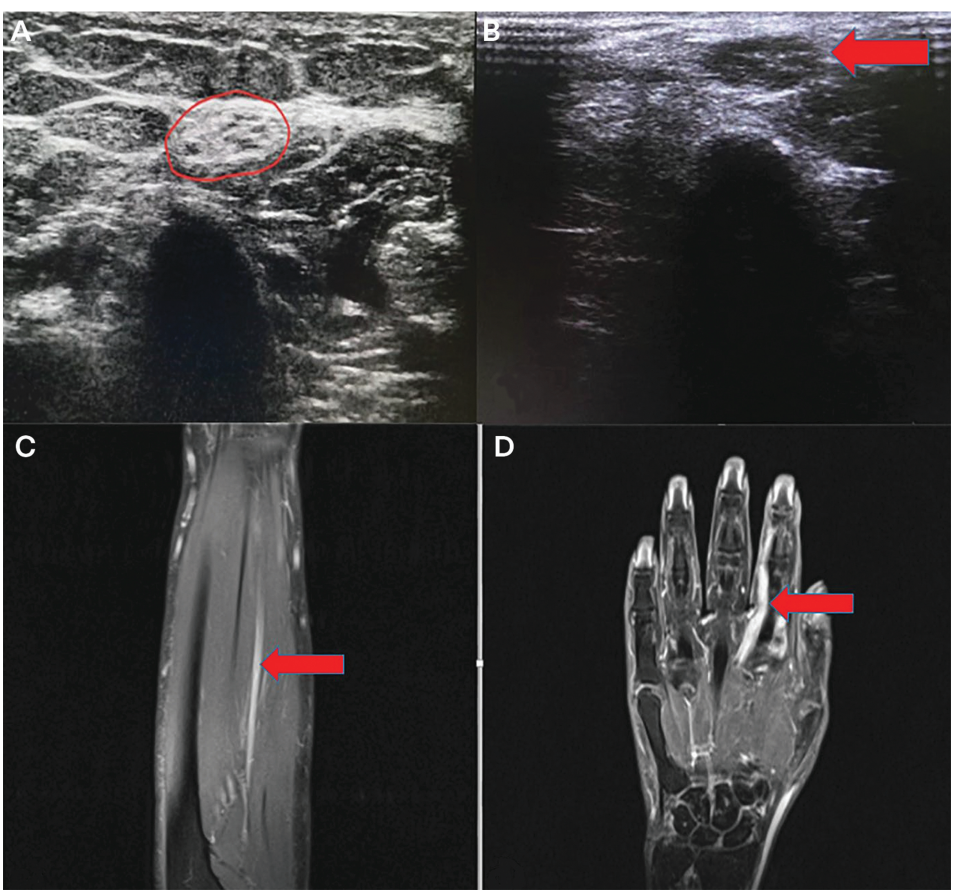

FIGURE 6-4

Radiologic evaluation of leprous neuritis. *A,* Ultrasonography of a normal ulnar nerve (*oval*). *B,* Ultrasonography of a leprous ulnar nerve with a hypoechoic area with focal thickening and loss of normal fascicular architecture (*arrow*). *C,* MR neurography showing thickening and contrast enhancement of the median nerve in the forearm (*arrow*). *D,* MR neurography showing thickening of the median digital branch in the palm and second digit (*arrow*).
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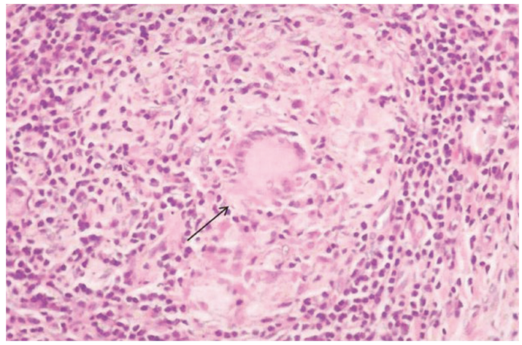

FIGURE 6-5
Superficial ulnar nerve biopsy showing a granuloma with a Langhans giant cell (*arrow*).
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The current recommendations are 6 months of therapy for paucibacillary cases and 12 months of therapy for multibacillary cases (TABLE 6-2). Clinicians should consult an infectious disease specialist for up-to-date treatment recommendations.

Lyme Disease

Lyme disease is the most common vector-borne illness in the United States and Europe and a common cause of neuropathies in both the acute and late stages of the illness. Lyme disease is caused by some species of spirochetes belonging to the genus *Borrelia burgdorferi sensu lato*. The genospecies *Borrelia burgdorferi sensu stricto* cause the majority of human illness in North America and Europe whereas *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia bavariensis* genospecies dominate infections in Europe and Asia.[108] Tick bites from the *Ixodes ricinus* species

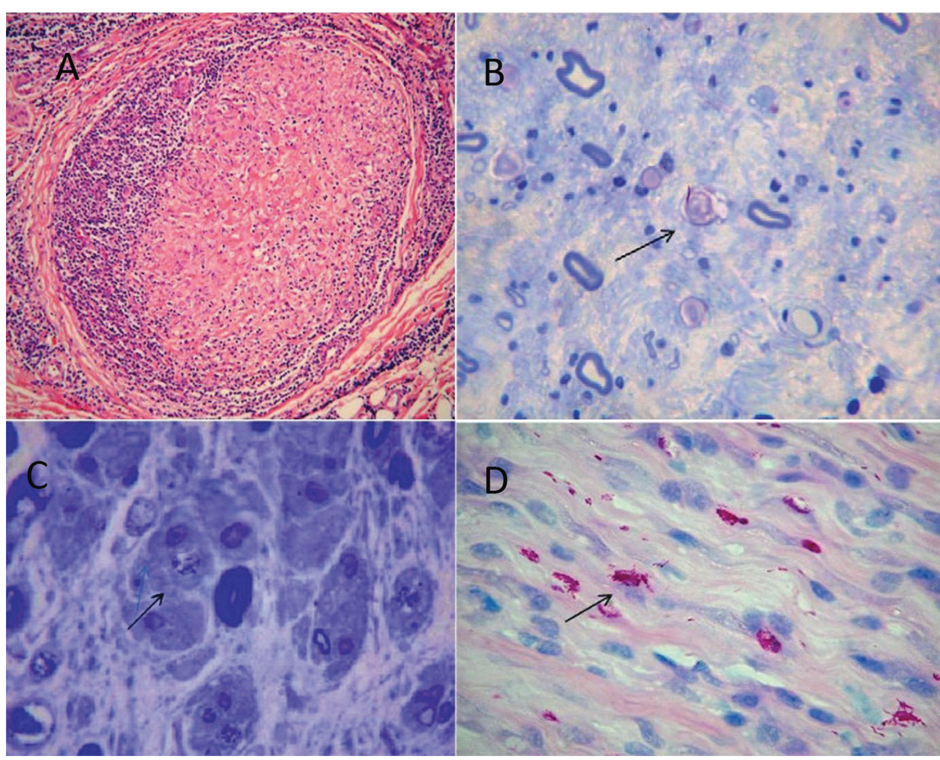

FIGURE 6-6
Images from a sural nerve biopsy in a patient with leprosy. *A*, Intense mononuclear infiltrate in the endoneurium, perineurium, and epineurium (hematoxylin and eosin [H&E] stain). *B*, A fascicle with loss of nerve fibers and axonal degeneration (*arrow*) (toluidine blue stain). *C*, *Mycobacterium leprae* seen as fine black dots inside a vacuolar cell (*black arrow*) (toluidine blue stain). *D*, Abundant acid-fast bacilli in groups or globi (*arrow*) (Wade stain).
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complex that are infected with *Borrelia* transmit Lyme disease by feeding on infected nonhuman reservoir hosts, including deer, mice, chipmunks, and other small mammals and birds. *Ixodes scapularis*, also known as the black-legged or deer tick is the principal vector in the United States, and an additional vector, *Ixodes pacificus*, is found in the western United States. *I. ricinus* and *Ixodes persulcatus* are the two tick species that most commonly transmit Lyme disease in Europe and Asia.[108] The majority of Lyme disease cases occur on the east coast and upper Midwest of the United States and in central Europe, where the ticks and spirochetes are endemic. However, with climate change, geographic dispersion of infected vectors, and other factors, Lyme disease is becoming more widespread.[109] Ticks can transmit the infection as a nymph or in the adult stages, but most cases of human transmission result from a bite of an infected nymph, given its small size. Nymphs are the size of a poppy seed (1 mm to 1.5 mm) and easily remain attached and unnoticed for the 24 to 48 hours required to transmit the infection to the human host.[110] Transfusion-related transmission and transmission through sexual contact, semen, urine, or breast milk have not been reported.[111]

Lyme disease is classified into three categories: early localized, early disseminated, and late stages. The classic presentation of early localized Lyme disease is an erythematous, nonpruritic, usually large (>5 cm) targetoid skin lesion, erythema migrans, that may expand over several days at the site of the tick bite.[112] The central clearing of erythema with peripheral enlargement causes the target or bull's-eye appearance, although it may be homogenous, lacking this central clearing, especially if treated early.[113] This lesion typically occurs within 5 to 30 days of infection and demonstrates the active proliferation of the spirochete, from which hematogenous spread occurs.[113] In some patients, this herald feature may not be present or may be missed if it occurs at sites that are not easily visible, such as the back, especially because it is nonpruritic. Manifestations of early disseminated Lyme infection include fever, headache, oligoarthritis or monoarthritis (especially affecting the knee), and carditis (the most common manifestation of which is fluctuating atrioventricular conduction block).[114,115]

Treatment of Leprosy TABLE 6-2

Regimen	Paucibacillary	Multibacillary
World Health Organization	Dapsone 100 mg daily Clofazimine 50 mg daily Rifampin 600 mg monthly Clofazimine 300 mg monthly Duration: 6 months	Dapsone 100 mg daily Clofazimine 50 mg daily Rifampin 600 mg monthly Clofazimine 300 mg monthly Duration: 12 months
US National Hansen's Disease (Leprosy) Program	Dapsone 100 mg daily Rifampin 600 mg daily Duration: 12 months	Dapsone 100 mg daily Rifampin 600 mg daily Duration: 24 months

Lyme disease can cause various neurologic symptoms, collectively known as *neuroborreliosis*. These symptoms typically occur within 1 to 2 months of infection.[116] One of the most recognized presentations of early disseminated Lyme disease is cranial neuropathy, with a predilection for the facial nerve. Patients develop unilateral or bilateral lower motor neuron facial palsies.[117] Less commonly, multiple cranial nerves can be affected and show enhancement on MRI.[118] In a systematic review, CSF pleocytosis was seen in only about a third of patients with Lyme-associated facial neuropathy, indicating that facial neuropathy can occur in the absence of meningitis. It also does not seem to involve the most proximal facial nerve since it typically spares the nerve to the stapedius, suggesting that meningitis may not cause the neuropathy although it may co-occur with it (CASE 6-2).[117]

Lyme meningitis may occur without cranial neuropathies and is characterized by headache and photophobia, although fever and meningeal signs may not be prominent.[119,120] Lyme radiculitis is another neurologic manifestation of early disseminated Lyme disease. It presents with pain, weakness, and paresthesia in

CASE 6-2

A 23-year-old Massachusetts man presented to the emergency department in mid-May with new onset left-sided headache and diplopia. His illness began 6 weeks before with low-grade fevers, myalgias, and fatigue, followed 2 weeks later by left facial weakness. He was seen by his primary care physician, who diagnosed him with Bell's palsy and treated him with a 21-day course of prednisone and valacyclovir, which resulted in some improvement. Shortly after he completed this regimen, he developed a left-sided headache and eye pain. Three days later, he developed horizontal binocular diplopia. On examination in the emergency department, there was mild orbital edema on the left, with ptosis and weakness of left eye closure. Visual acuity was normal. The left pupil was slightly larger than the right. There was limited abduction of the left eye, and pain accompanied his eye movements. There was mild bilateral optic disc edema. Facial sensation and the remainder of the cranial nerve and neurologic examination were unremarkable. MRI of the brain showed bilateral optic neuritis and perineuritis, which were worse on the left. He underwent an extensive serologic workup. A lumbar puncture was performed, and CSF revealed mild lymphocytic pleocytosis (8 cells/mm^3) with normal protein, glucose, and cytology. His Lyme immunoblot was positive, and his CSF Lyme disease index was elevated, consistent with neuroborreliosis. He was treated with IV ceftriaxone, which significantly improved his headache and eye pain. He was discharged from the hospital on a 1-month course of doxycycline. At his 6-week follow-up appointment all of his symptoms had resolved.

COMMENT

This case illustrates Lyme neuroborreliosis presenting with multiple cranial neuropathies. The patient had no history of tick bites or known history of erythema migrans, emphasizing the need to consider a Lyme diagnosis in the absence of known exposure or skin rash.

one or more extremities and, despite the name, represents a mononeuropathy multiplex rather than radiculopathy. A high index of suspicion is necessary because the radiculitis can manifest with only sensory symptoms without motor deficits.[121] Lymphocytic meningoradiculitis, or Bannwarth syndrome, consists of a triad of painful radiculitis, multifocal motor deficits including facial palsy or other cranial neuropathies, and CSF lymphocytic pleocytosis. This is a common presentation of early Lyme neuroborreliosis in Europe.

Peripheral nervous system complications of late Lyme disease include intermittent paresthesia with sensory neuropathy on electrodiagnostic testing, facial neuropathy, radiculitis, and mononeuropathy multiplex. The pathophysiology is largely axonal.[122] Late Lyme disease can mimic vasculitic mononeuritis multiplex, with focal weakness and sensory changes in the distribution of multiple peripheral nerves.[123] Acrodermatitis chronica atrophicans is a chronic dermatologic syndrome caused by an untreated *B. afzelii* infection and is more commonly seen in Europe than in North America. It is characterized by cutaneous atrophy in the distal extremities. If untreated, it can progress from an initial bluish-red skin discoloration to inflammation of the area, followed by atrophy and fibrosis of the skin in the involved regions. It is associated with a distal, predominantly sensory, axonal neuropathy.[124] Demyelinating neuropathy similar to GBS or CIDP is rarely reported in the context of Lyme disease, which may reflect chance association.[125] For a detailed review of the neurologic complications of Lyme disease, including central nervous system disorders, refer to the August 2021 *Continuum* issue on neuroinfectious disease.[126]

The diagnosis of Lyme disease rests upon the identification of antibody responses against *B. burgdorferi* in serum. A two-tiered testing protocol has been the standard for nearly 30 years.[127] First, serum is analyzed with a sensitive enzyme immunoassay (EIA) or immunofluorescent assay for IgG and IgM antibodies to *Borrelia*. If this is positive or equivocal, testing automatically reflexes to standardized IgM and IgG Western blot.[127] In 2019, the US Food and Drug Administration (FDA) updated the testing recommendations allowing an EIA instead of the Western blot as the second test in the algorithm. Thus, serologic tests using a second EIA that targets different antigens in place of the Western blot are acceptable alternatives for diagnosing Lyme disease.[128] The time from symptom onset to serologic testing can affect the results, and early testing may lead to false negatives. In the setting of clinical symptoms consistent with Lyme disease and negative early testing, recent guidelines recommend repeat testing 1 month from the start of symptoms.[129]

Despite the frequency of tick bites in endemic areas, the risk of developing Lyme disease after a single tick bite is low, ranging from 2.6% to 3.2%, increasing to 6.7% if a tick tests positive for *Borrelia burgdorferi* DNA.[130,131] Postexposure prophylaxis with a single dose of doxycycline 200 mg given orally within 72 hours of exposure has been shown to reduce the rate of infection from 3.2% to 0.4% with 87% efficacy, but it did cause more adverse effects than placebo, mainly nausea and vomiting.[131] Per the US Centers for Disease Control and Prevention, the benefit of prophylaxis may outweigh the risks when all of the following are present: the bite occurred in an area where ticks are likely to be infected, the tick was removed in the previous 72 hours, the tick was an *Ixodes* tick with an engorged body (with blood), and doxycycline is safe for the patient.[132] Recent guidelines recommend antibiotic prophylaxis with one dose of oral doxycycline within 72 hours of tick removal after a high-risk bite.[133]

KEY POINTS

- **Lyme disease is the most common vector-borne illness in the United States and Europe, where ticks and spirochetes are endemic. Climate change is leading to a more widespread geographic dispersion of Lyme disease.**

- **Although facial neuropathy is the most frequent cranial neuropathy in early disseminated Lyme disease, patients can present with multiple cranial neuropathies.**

- **Early serologic testing for Lyme disease may return a false-negative result. When early testing is negative and clinical symptoms are suggestive, the clinical recommendation is to retest in 1 month from the start of symptoms.**

Recent guidelines also provide recommendations for the treatment of Lyme disease. Erythema migrans should be treated with a 10-day course of doxycycline 100 mg 2 times a day or a 14-day course of either amoxicillin 500 mg 3 times a day or cefuroxime axetil 500 mg 2 times a day. For acute neurologic manifestations of Lyme disease, a 14-day to 21-day course of IV ceftriaxone 2 g daily, cefotaxime, penicillin G, or oral doxycycline is recommended. The latest evidence-based guideline provides an extensive review and several other recommendations.[133,134] No difference in patient outcomes has been found in patients treated with oral doxycycline compared with IV ceftriaxone in acute neuroborreliosis.[135] A phase 3 clinical trial for a prophylactic Lyme disease vaccine is underway in North America and Europe.[136]

CONCLUSION

A multitude of infectious agents can cause various types of peripheral neuropathies, and it is important to recognize and treat them to reduce morbidity. Although studies have found an association between COVID-19 and several neurologic acute complications and possibly long-term sequelae, these studies, performed in the setting of a serious pandemic, and ongoing clinical studies combined with basic research into the pathogenesis of these disorders are necessary before establishing causation.

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DISCLOSURE

Continued from page 1418

board member for *Muscle & Nerve*; and in the range of $10,000 to $49,999 for serving as a consultant for UCB, Inc. Dr Narayanaswami has stock in Doximity, Inc, Dr Reddy's Laboratories Ltd, Moderna, Inc, Pfizer Inc, and Viatris Inc. Dr Narayanaswami has noncompensated relationships as a member of the boards of directors with the American Association of Neuromuscular & Electrodiagnostic Medicine and the Myasthenia Gravis Foundation Of America, Inc, that are relevant to American Academy of Neurology interests or activities. The institution of Dr Narayanaswami has received research support from Alexion Pharmaceuticals, Inc.

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Toxic Neuropathies

By Brendan L. McNeish, MD; Noah Kolb, MD

ABSTRACT

OBJECTIVE: The purpose of this article is to provide an overview and update on the most clinically relevant toxic neuropathies.

LATEST DEVELOPMENTS: Broadly, toxic neuropathies were previously quite rare with the notable exception of neuropathy from alcohol or older chemotherapeutics. The development of newer therapies, particularly immunotherapy to treat malignancy, has resulted in a substantial increase in the occurrence of toxic neuropathies that require timely recognition and treatment. The understanding of other toxic neuropathies continues to evolve, such as statin-induced neuropathy, which new evidence suggests is much less common than previously suspected.

ESSENTIAL POINTS: Toxic neuropathies can be caused by medications, supplements, and recreational substances that injure peripheral nerves. Medications have evolved in the past 2 decades, as have the types of neuropathies that can be seen as related toxicities. In some areas of medicine, new classes and generations of drugs are associated with a lower incidence of toxic neuropathy.

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Address correspondence to Dr Noah Kolb, 1 S Prospect St, MS 405AR2, Burlington, VT 05401, Noah.kolb@uvmhealth.org.

RELATIONSHIP DISCLOSURE:
Dr McNeish has received research support in the range of $100,000 to $499,999 from the National Institutes of Health (NIA P30AG02482). Dr Kolb has received personal compensation in the range of $0 to $499 for serving as a consultant for Eisana Corp; in the range of $500 to $4999 for serving as a consultant for Abalone Bio, Inc, Alexion Pharmaceuticals, Inc, Lilly, and UCB S.A.; in the range of $5000 to $9999 for serving as a consultant for the National Institute of Neurological Disorders and Stroke and as an expert witness for Locks Law and Ralston, Pope & Diehl; and in the range of $10,000 to $49,999 for serving as an expert witness for Walkup, Melodia, Kelly & Schoenberger. The institution of Dr Kolb has received research support from the National Cancer Institute.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs McNeish and Kolb discuss the unlabeled/investigational use of baclofen-amitriptyline-ketamine, gabapentin, lidocaine, mexiletine, nortriptyline or amitriptyline, and pregabalin for the treatment of neuropathic pain.

INTRODUCTION

Toxic neuropathies can occur from a wide variety of sources, including medications, vitamins, and recreational substances that injure peripheral nerves. As medications have evolved in the past 2 decades, so too have the types of neuropathies that can be seen as associated toxicities. In some areas of medicine, such as infectious disease, new classes and generations of drugs, such as antiretrovirals for human immunodeficiency virus (HIV), are associated with a lower incidence of toxic neuropathy. In contrast, the widespread use of immunotherapy in cancer treatment has dramatically improved cancer care but has resulted in a substantial increase in toxic neuropathies associated with the newer class of antineoplastic agents known as immune checkpoint inhibitors (ICIs).

This article will focus on toxic neuropathies that are increasing in prevalence, commonly seen in clinical practice, or likely to alter clinical decision making when identified. Broadly speaking, these include neuropathies caused by cancer therapies (immunotherapy and chemotherapy), immunosuppressants, cardiovascular medications, antimicrobials, antiseizure medications, and heavy metals. Neuropathy caused by alcohol, industrial agents, solvents, biologic agents, and venoms will not be discussed.

IMMUNE CHECKPOINT INHIBITOR–RELATED NEUROPATHY

Since 2011, ICIs have increasingly been used to treat malignancy.[1–3] ICIs improve survival in many advanced diseases, but their use is associated with immune-related adverse events. Overall, neurologic immune-related adverse events are relatively uncommon, with an incidence of 1% to 12%, but can have serious implications because of their associated morbidity and mortality.[4]

Among the neurologic immune-related adverse events, it is estimated that 75% affect the peripheral nervous system and 25% are associated with central nervous system toxicity.[5] Specific to this review, toxic neuropathies comprise 29% of neurologic immune-related adverse events.[5] Overlap of immune-related adverse events across both the peripheral and central nervous systems, as well as other organ systems, is very common. This overlap can present diagnostic challenges. For example, a patient with multiple immune-related adverse events could present with facial weakness from facial neuropathy, arm weakness from myositis, and abdominal pain from autoimmune hepatitis. This highlights the need for a broad differential and workup when immune-related adverse events are suspected. Because of the complexity of the neurologic presentation and frequency of overlap syndromes, the American Society of Clinical Oncology (ASCO) has recommended that neurologists participate in team-based clinical care for the diagnostic workup and management of neurologic immune-related adverse events.[6] In the following paragraphs, the pathophysiology, presentations, and clinical management of ICI-related neuropathy will be summarized. ICI-related neuropathy is projected to become increasingly common now that 40% of patients with cancer are eligible for ICI therapy.[7]

The current ICIs are monoclonal antibodies that downregulate checkpoints of the immune system and, thereby, increase the surveillance of the immune system to detect foreign cells, including cancer cells. The three classes of ICIs are (1) programmed cell death protein-1 (PD-1) inhibitors, (2) ligand of PD-1 (PD-L1) inhibitors, and (3) cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors. PD-L1 inhibitors, such as atezolizumab, and PD-1 inhibitors, such as nivolumab, are mechanistically equivalent in ultimately targeting PD-L1, which cancer cells upregulate to evade detection and destruction by the immune system. Therefore, their adverse effects are commonly categorized together. CTLA-4 inhibitors, such as ipilimumab, block the CTLA-4 receptors on activated T cells preventing downregulation of the activated state (FIGURE 7-1[8]). Oncologists use both single-agent and combination ICI therapy since the CTLA-4 and PD-L1 immunotherapies target different immune checkpoints. Inhibition of these immune checkpoints causes the immune system to identify more cancer cells but also increases the potential for misrecognition of self-antigens, causing autoimmune conditions manifesting as immune-related adverse events. The CTLA-4, PD-1, and PD-L1 inhibitors, alone and in combination, have been implicated in causing a wide variety of ICI-related neuropathy presentations.

ICI-related neuropathy can present in multiple ways. This phenotypic diversity is driven by various potential localizations within the peripheral nervous system, types of fibers affected (small or large and sensory, motor, or autonomic), and the underlying structural pathophysiology (demyelinating, axonal). Because of limited data, it is difficult to estimate the exact prevalence of the various ICI-related neuropathy phenotypes. A 2021 systematic review of ICI-related neuropathies (n = 125) reported the following estimates: acute or subacute demyelinating neuropathy (25%), cranial neuropathies (25%), acute

KEY POINTS

- Immune checkpoint inhibitor-related neuropathy is projected to become more prevalent because more cancers are becoming eligible for immune checkpoint inhibitor therapy.

- Immune checkpoint inhibitor-related neuropathy can present with a broad spectrum of phenotypes determined by the components of the peripheral nervous system targeted by the immune system.

- Immune checkpoint inhibitor-related neuropathy incidence increases when ligand of programmed cell death protein-1 and cytotoxic T-lymphocyte-associated antigen 4 therapies are combined.

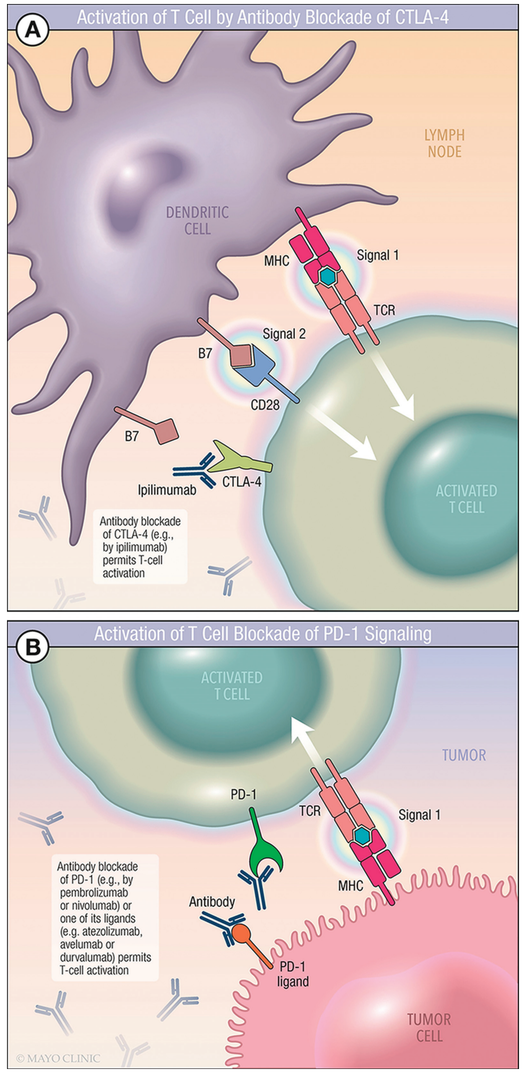

FIGURE 7-1

Mechanism of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) signaling in immune response. *A*, CTLA-4 receptor on activated T-cell is the target for anti–CTLA-4 therapy. *B*, PD-1 and ligand of PD-1 (PD-L1) proteins on the activated T cell and tumor cell, respectively, are the targets for anti-PD-1 and anti–PD-L1 therapy.

MHC = major histocompatability complex; TCR = T-cell receptor.

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axonal motor or sensorimotor neuropathies (13%), unspecified polyradiculoneuropathy (13%), sensory neuropathy or neuronopathy (8%), chronic inflammatory demyelinating neuropathy (6%), Miller Fisher syndrome (3%), phrenic neuropathy (2%), isolated enteric neuropathy (2%), vasculitic neuropathy (1%), motor neuropathy (1%), and mononeuritis multiplex (1%).[5] In summary, ICI-related neuropathy is very diverse with a possible predilection for Guillain-Barré syndrome (GBS)-like neuropathies and cranial neuropathies. Melanoma (66%) followed by non–small cell lung cancer (14%) are the cancer types most frequently reported with ICI-related neuropathy, but it should be noted that this representation could change as ICI therapy is expanded to more types of cancer. Although PD-L1 ICI therapy is the most common cause of ICI-related neuropathy, this is likely because of its broad use in multiple malignancies. It is important to point out that the incidence of most neurologic immune-related adverse events increases with the combination of PD-L1 and CTLA-4 therapy.[9]

There are two general mechanisms for ICI-related neuropathy. The first, and most common, mechanism is that ICI therapy increases the native immune system's misrecognition of self (in this case, peripheral nerve). The second mechanism is that, with decreased regulation, the immune system generates a paraneoplastic syndrome in response to the cancer that secondarily attacks the peripheral nerve targets. Immune-related neuropathies in patients with neuroendocrine tumors are more likely to reflect paraneoplastic syndromes. These induced paraneoplastic ICI-related neuropathies can present with sensory

neuronopathy and have a higher association with onconeural antibodies such as anti-Hu/antineuronal nuclear antibody type 1 (ANNA-1) and collapsin response mediator protein-5 (CRMP-5)/anti-CV2.[5,10]

Identifying a paraneoplastic mechanism in patients with ICI-related neuropathy is clinically relevant because neuropathies associated with paraneoplastic syndromes also require immunosuppression, but definitive treatment requires addressing the underlying malignancy and may change the prognosis.[10]

Although the phenotypic presentations are quite diverse, ICI-related neuropathies share the timing of presentation after ICI treatment and associated risk factors. ICI-related neuropathies generally present acutely or subacutely 8 to 12 weeks or two to three cycles after ICI initiation or with the addition of a novel ICI.[11] However, there have been reports of ICI-related neuropathy occurring as late as 6 months after ICI initiation. The understanding of risk factors for immune-related adverse events is limited, but the consensus among experts is that preexisting autoimmune conditions are related to the development of neurologic immune-related adverse events, including ICI-related neuropathy.[12] Specific cancers have been associated with increased neurologic immune-related adverse events; however, it is not known if this is due to the cancer itself, past treatment, or an unidentified intrinsic risk factor. Of note, it is unknown if a preexisting neuropathy, for example, from diabetes, chemotherapy, or preexisting autoimmunity, increases the risk of ICI-related neuropathy because research studies to date have traditionally excluded patients with preexisting neuropathies.

The diagnosis of ICI-related neuropathy can be difficult, given the variety of presentations and the possibility of overlap of immune-related adverse events. Furthermore, these patients often have additional risk factors for other forms of neuropathy such as diabetes, neurotoxic chemotherapy exposure, or vitamin deficiencies. Despite these challenges, a detailed history and neurologic examination are the foundation on which to build a clinical suspicion for an ICI-related neuropathy. Specifically, a history of an acute or subacute presentation in the setting of recent ICI initiation or the addition of a second ICI will differentiate this entity from most other neuropathies. The examination is critical to identify the neuropathy, but depending on the presentation, the findings of significant weakness (particularly proximal) or involvement of a cranial nerve would favor an ICI-related neuropathy as opposed to a typical length-dependent chemotherapy-induced peripheral neuropathy (CIPN) presentation. Reflex examination can also help to differentiate central from peripheral neurologic immune-related adverse events or to distinguish neuropathy from myopathy, although these can occur simultaneously.

Once ICI-related neuropathy is suspected based on the history and examination, further workup, including laboratory tests, imaging, electrodiagnostic studies, CSF testing, and a nerve biopsy (in rare cases), can help secure the diagnosis. There are no definitive consensus guidelines for diagnostic workup, but Guidon and colleagues[11] published a comprehensive algorithmic workup for suspected ICI-related neuropathy that takes into account the severity of the neuropathy. Laboratory tests, imaging, and CSF studies should be ordered based on the presentation. Unlike other forms of GBS, patients with ICI-related acute inflammatory demyelinating polyradiculoneuropathy are more likely to have CSF pleocytosis.[5]

KEY POINTS

- In cases of severe sensory neuropathy or neuronopathy in patients on immune checkpoint inhibitors, it is important to screen for paraneoplastic syndromes.
- Because of phenotypic heterogeneity, recognizing the acute onset of neurologic deficits and temporal relationship to immune checkpoint therapy are critical for the diagnosis of an immune checkpoint inhibitor-related neuropathy.

CSF studies are also useful to evaluate for mimickers of ICI-related neuropathy such as leptomeningeal metastasis. In the setting of a cranial neuropathy, MRI studies may be beneficial because enhancement of nerves is frequently visualized and can rule out structural causes.[10] Grading of ICI-related neuropathy is summarized in TABLE 7-1[11] and evaluation recommendations are summarized in TABLE 7-2.[6,11]

Within the diagnostic workup, EMG with nerve conduction studies is essential to localize the neuropathy, characterize the affected modality, differentiate between axonal and demyelinating pathology, and identify overlap syndromes such as myositis and myasthenia gravis. Myositis and myasthenia gravis are particularly important to recognize as they have strong associations with myocarditis and a poor prognosis.[13] An electrodiagnostic finding that fails to demonstrate large fiber involvement in the setting of a suspected neuropathy should prompt consideration of a small fiber neuropathy with the possibility of autonomic involvement.

Some cases of ICI-related GBS differ from classic forms. In these patients, nerve conduction studies may demonstrate a pattern more consistent with axonal pathology; however, biopsy of nerve fibers reveals disruption of the myelin from an immune process.[14] In summary, laboratory tests, imaging, and tests to support a diagnosis of ICI-related neuropathy should be tailored from a

TABLE 7-1

Grading of Immune Checkpoint Inhibitor-related Neuropathy[a]

Severity grade (Common Terminology Criteria for Adverse Events equivalent)	Associated features
1-Mild	Mild sensory symptoms
2-Moderate	Any weakness from neuropathy, but gait is maintained Interference with lower extremity activities of daily living Neuropathic pain requiring nonopioid pain medication All cranial neuropathies
3-Severe	Impaired ambulation due to weakness or impaired proprioception Limited upper-extremity activities of daily living Neuropathic pain refractory to nonopioid medications and limited activities of daily living Dyspnea not requiring invasive or noninvasive ventilation
4-Fulminant	Intubation or noninvasive ventilation for respiratory weakness Feeding tube placement for dysphagia
5-Death	Death due to respiratory failure from bulbar muscle weakness

[a] Modified with permission from Guidon AC, et al, J Immunother Cancer.[11] © 2021 BMJ Publishing Group Ltd & Society for Immunotherapy of Cancer.

Guide for Workup and Management of Immune Checkpoint Inhibitor-related Neuropathy Based on Presentation and Grade[a,b]

TABLE 7-2

	Possible peripheral neuropathy		Possible Guillain-Barré syndrome	
Grade	**Workup**	**Management**	**Workup**	**Management**
1	Laboratory tests: hemoglobin A_{1C}, vitamin B_{12}, serum protein electrophoresis, immunofixation, serum free light chain assay, creatine phosphokinase	Neurology consultation	Proceed to grade 2	Proceed to grade 2
2	Laboratory tests: per neuropathy phenotype, consider tests for grade 1 plus paraneoplastic panel, antinuclear antibody, antineutrophilic cytoplasmic antibody, rheumatoid factor, Sjögren syndrome A and B (SSA, SSB), ribonucleoprotein, anti–double-stranded DNA antibodies, erythrocyte sedimentation rate, C-reactive protein, anti-GM-1 antibodies, anti–myelin-associated glycoprotein (MAG), Lyme disease, human immunodeficiency virus (HIV), hepatitis B and C Imaging: MRI of the spine with and without contrast, MRI of the brain if cranial involvement, MRI of the plexus if appropriate Other: electrodiagnostic testing	Hold immune checkpoint inhibitors Consider oral prednisone (0.5-1 mg/kg) if progressing Neuropathic pain control: see TABLE 7-3	Laboratory tests: serum anti-GM1 antibodies, anti-GQ 1b ganglioside antibodies (Miller Fisher presentation), paraneoplastic panel, flow cytometry in hematologic malignancies, consider other laboratory tests from workup of peripheral neuropathy CSF testing: protein, cell count and differential cell count, glucose, cytology, cultures, oligoclonal bands Imaging: MRI of the spine with and without contrast Other: electrodiagnostic testing	Admit patient to the hospital, discontinue immune checkpoint inhibitors Neurology consultation Initiate intravenous immunoglobulin (IVIg), plasma exchange or IV methylprednisolone (2-4 mg/kg/d) or pulse dose oral steroid (1 mg/kg/d for 5 days) (steroid regimens are followed by a taper) Frequent neurologic checks Pulmonary function testing (negative inspiratory force, forced vital capacity) Monitor for autonomic fluctuations (ie, blood pressure and heart rate) as well as for constipation and ileus Neuropathic pain control: see TABLE 7-3
3 and 4	Follow the above algorithm for peripheral neuropathy and include Guillain-Barré syndrome (GBS) algorithm for grades 2-3	Admit patient to the hospital Neurology consultation Permanently discontinue immune checkpoint inhibitors Initiate IV methylprednisolone (2-4 mg/kg/d) Proceed with management per GBS algorithm for grades 2-3	Iterative process, keep differential open with special consideration of overlap syndromes and paraneoplastic involvement	Manage with multidisciplinary approach consisting of neurology, critical care, and oncology teams Consult physical therapist, occupational therapist, speech-language pathologist, and physical medicine and rehabilitation specialist for appropriate rehabilitation recommendations

CFS = cerebrospinal fluid; DNA = deoxyribonucleic acid; IV = intravenous; MRI = magnetic resonance imaging.

[a] Data from Schneider BJ, et al, J Clin Oncol[6] and Guidon AC, et al, J Immunother Cancer.[11]

[b] The workup and management of immune-related neuropathy is divided by presentation of possible GBS versus other peripheral neuropathy, and it is further divided by the grade of the presentation. For information on grades of presentation, see TABLE 7-1.

KEY POINTS

- Because of the diversity of neurologic involvement, a standardized diagnostic and treatment algorithm is recommended in evaluating patients with suspected immune checkpoint inhibitor-related neuropathies.

- Selecting the correct treatment for immune checkpoint inhibitor-related neuropathy relies on accurately grading the severity of the presentation.

- Unlike other forms of Guillain-Barré syndrome, patients with immune checkpoint inhibitor-related acute inflammatory demyelinating polyradiculoneuropathy respond to treatment with corticosteroids and are more likely to have CSF pleocytosis.

- It is unclear whether immunosuppression for immune checkpoint inhibitor-related neuropathy changes cancer prognosis and whether rechallenge of immune checkpoint inhibitor therapy should be considered in these patients.

comprehensive history and examination. It is also clinically important to identify paraneoplastic neuropathies.

Despite the diverse clinical phenotypes of immune-related adverse events, ASCO has recommended a common approach to the management of immune-related adverse events, including ICI-related neuropathy, that is based on the degree of immune-related adverse events–related disability.[6] The degree of disability is measured by the Common Terminology Criteria for Adverse Events on a scale of 1 to 5.[6,11,15] Grade 1 disability is mild involvement and grade 5 correlates with death, summarized in TABLE 7-1.[6] It is recommended that a multidisciplinary team is involved with all grades of immune-related adverse events because of the potential of multiple organ systems being involved and the importance of weighing the anticancer benefit of the ICI. With grade 1 disability, it is recommended that a neurologist participates in the workup of ICI-related neuropathy. At a grade of 2, which includes any degree of weakness, it is recommended that there is consideration of a pause of the ICI (TABLE 7-1 and TABLE 7-2). Cessation of the ICI and immunosuppression using corticosteroids is recommended when a patient has grade 3 or 4 immune-related adverse events–related disability, and 60% of these patients improve within 4 weeks.[5,11] If the patient's condition continues to decline, other methods of immunosuppression, such as intravenous immunoglobulin (IVIg), plasma exchange, rituximab, and infliximab can be considered.[6] Although management of immune-related neuropathy generally follows treatment paradigms similar to inflammatory neuropathies, a notable difference is that GBS-like presentations of immune-related neuropathy may respond to corticosteroids (CASE 7-1).

The prognosis of ICI-related neuropathy is dependent on several variables, including the neuropathy phenotype, severity, and presence of other immune-related adverse events. In general, 70% to 80% of patients with ICI-related neuropathy partially or fully improve; however, approximately 10% of the GBS-like presentations are fatal.[5] It is essential to be thoughtful about immunosuppression in patients with neurologic immune-related adverse events because there is a theoretical risk that medications such as corticosteroids reduce the anticancer ICI effect. In patients whose ICI-related neuropathy improves after ICI discontinuation, a common question is the risk of restarting ICI therapy. Although restarting ICI therapy is generally considered when immune-related adverse events–related disability improves to grade 1, there are no guidelines or compelling evidence to guide management in restarting ICI therapy after an improved or resolved neuropathy.[11] Clinical experts recommend careful discussion between the managing neurologist, oncologist, and patient about the risks and benefits of restarting ICI therapy.[14] The use of immunosuppression during retrial is generally not recommended because of the risk of reducing the anticancer activity of the ICIs.

Given the novelty of ICI therapy and lack of detailed outcomes of patients with ICI-related neuropathy, little is known about the specific morbidity and disability prognosis. Interestingly, many noncardiac and non-neurologic immune-related adverse events are associated with improved survival.[16,17] The reasoning is that immune-related adverse events provide evidence that the immune system has truly been activated. However, this is not the case for neurologic immune-related adverse events, which are associated with a worse prognosis.[18] With the increasing use of ICIs in more cancer types and milder

disease, more research is needed to better understand the long-term effects and the ongoing needs of this expanding patient population.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

CIPN is a common, length-dependent, toxic neuropathy that occurs from neurotoxic chemotherapy treatment.[19] It occurs in 40% to 60% of patients who are exposed to these agents and is the most common cause of chemotherapy reduction or cessation.[20] CIPN's prevalence and importance continue to grow

CASE 7-1

A 72-year-old woman with melanoma and diabetes without prior neuropathy presented to the emergency department with lower-extremity weakness, numbness, and bandlike low back pain. Ten days before presentation, she had completed her first cycle of nivolumab. Three days before presentation, she noted numbness in her feet and gait instability, which rapidly progressed to weakness in both of her legs. Her examination demonstrated global areflexia; proximal and distal weakness in the lower, more than upper, extremities; and reduced sensation to all sensory modalities from the thighs down. Contrasted MRI revealed lumbar spinal nerve root enhancement along with patchy enhancement of the lumbar paraspinal muscles. Lumbar puncture showed an elevated CSF protein level at 130 mg/dL and 35 nucleated cells/mm^3. Her creatine kinase level was 600 U/L. She was admitted to the hospital for suspected acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and myositis related to nivolumab therapy. Electrodiagnostic studies revealed a demyelinating neuropathy with fibrillation potentials and small, complex motor unit potentials in the paraspinal muscles. Within 12 hours of admission, her upper extremity weakness worsened. Her cardiac workup was normal including an ECG, echocardiogram, troponin, and brain natriuretic peptide.

Nivolumab was stopped and she was treated with IV methylprednisolone (1 g daily for 5 days) and IVIg 2 g/kg, administered in divided doses over 5 consecutive days. Treatment resulted in substantial improvement in both her weakness and numbness, and she was ultimately discharged with a steroid taper. As an outpatient, she made a nearly full recovery at 3 months, but her oncologist opted not to continue nivolumab.

COMMENT

This case demonstrates some of the characteristics of ICI-related AIDP that distinguish it from classic GBS. The lumbar puncture showed increased numbers of nucleated cells, which can be seen in ICI-related AIDP but would be atypical for classic AIDP. Additionally, she had a superimposed myositis that was identified through the combination of MRI, EMG, and laboratory evaluation. Finally, and perhaps most importantly, unlike patients with classic GBS, patients with ICI-related AIDP can improve with high-dose steroids.

KEY POINTS

- Chemotherapy-induced peripheral neuropathy is the most common dose-limiting side effect of neurotoxic chemotherapy.
- The phenotype of chemotherapy-induced peripheral neuropathy varies widely depending on the causative agent.

with the increased use of chemotherapy and improved cancer survival.[21] Early recognition and management of CIPN are critical because CIPN is associated with acute and chronic impairments in physical and psychological function; increased risk for falls, fractures, and disability; and a decreased quality of life.[22-25] CIPN affects not only individual cancer survivors but the whole health system; compared with cancer- and chemotherapy-matched controls, health care for patients with CIPN costs $20,000 per year more than health care for cancer survivors without CIPN.[26]

Improved recognition and management of CIPN is critical given the increasing population of cancer survivors, now totaling more than 18.5 million in the United States, many of whom received neurotoxic chemotherapy.[27]

Generally, CIPN presents as a length-dependent, sensory greater than motor, axonal neuropathy in the setting of treatment with chemotherapy. Sensory fibers are typically affected first, involving small or large fibers, and the degree of motor and autonomic involvement is highly dependent on the specific agent (FIGURE 7-2).[28] Symptoms generally develop toward the end of a chemotherapy regimen as the cumulative dose increases.

The risk factors for developing CIPN are inadequately understood, largely because of the retrospective nature of many studies, the heterogeneity of definitions for CIPN, and the range of chemotherapy agents causing CIPN. Generally, it is thought that older age, African American race, diabetes, higher body mass index, and preexisting neuropathy are risk factors for developing CIPN.[29-32] There are some well-defined, albeit very specific, genetic risk factors as well. For instance, those with a genetic predisposition to slowed metabolization of vincristine are at increased risk of CIPN when exposed to vincristine. Charcot-Marie-Tooth (CMT) neuropathy, specifically CMT1A (caused by *PMP22* duplication), is considered a contraindication to vinca alkaloid therapy because of increased susceptibility to neurotoxicity.[33] Increased susceptibility for neurotoxicity in other CMT types and other neurotoxic chemotherapy agents has not been clearly established.[34-36] CIPN can unmask previously unidentified cases of CMT, but further research is needed to better understand this relationship.[37,38]

Diagnosis of CIPN is based on the presenting clinical history, physical examination, and

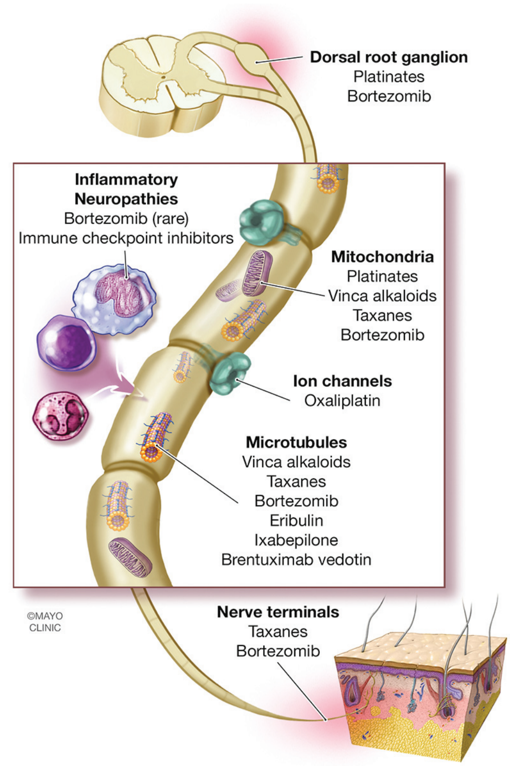

FIGURE 7-2
Structural mechanisms of neurotoxicity of chemotherapy agents.
Reprinted with permission from Staff NP, Continuum (Minneap Minn).[28] © 2020 American Academy of Neurology.

consideration of potential mimickers. Generally, patients present with a subacute, symmetric, length-dependent, sensory greater than motor neuropathy that starts after neurotoxic chemotherapy treatments.[39] Of note, there are important exceptions to these diagnostic criteria for specific chemotherapy agents that will be discussed later in this section. In clear cases of suspected CIPN, it is reasonable to rule out common causes of length-dependent neuropathy such as vitamin B_{12} deficiency, diabetes, and paraproteinemia with a decreased vitamin B_{12} level or elevated methylmalonic acid, hemoglobin A_{1C}, and serum protein electrophoresis with immunofixation, respectively. In cases of possible CIPN, where the presentation is more acute, severe, or does not follow a length-dependent distribution, a broader workup is recommended. Important mimickers of CIPN are cancer-related neuropathies, especially from monoclonal proteins, paraneoplastic syndromes, or other medications such as ICIs.

Additional workup that could be considered when there is less clarity about a diagnosis of CIPN would include electrodiagnostic testing, laboratory testing, and skin or nerve biopsy. Laboratory testing can be used to identify mimickers of CIPN, including vitamin deficiencies, paraproteinemic neuropathies, and paraneoplastic neuropathies. Testing should include evaluation of vitamin levels to identify B_1 and B_{12} deficiency as well as B_6 toxicity. It should be noted that vitamin B_6 can be used to treat nausea, commonly reported by patients with cancer, and excess vitamin B_6 can cause a sensory neuronopathy that may present like CIPN. Paraproteinemic neuropathies can be related to monoclonal gammopathy from malignancy such as multiple myeloma, which can present similarly to CIPN. Moreover, plasmacytomas are associated with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome; often demonstrate lambda monoclonal proteins on immunofixation; and should prompt serologic testing for vascular endothelial growth factor (VEGF), which is both sensitive and specific for POEMS syndrome.[40]

Platinum-based chemotherapeutics preferentially affect the dorsal root ganglion and consequently can present with a sensory neuronopathy. For patients in whom the etiology of neuronopathy is unclear, serologic testing for paraneoplastic mechanisms should include anti-Hu/ANNA-1 and CRMP-5/anti-CV2 antibodies.[41] Overall, the laboratory workup for CIPN should be directed by the level of suspicion for CIPN based on the presenting history and physical examination.

Electrodiagnostic testing can be helpful in complicated cases but is not required for most patients with CIPN. EMG and nerve conduction studies can distinguish pathophysiology (ie, demyelinating versus axonal), distribution, severity, and localization of the neuropathy. Similarly, no evidence supports regular monitoring of CIPN severity with electrodiagnostic testing, and the patient's symptoms and examination are usually sufficient guides.

Skin and nerve biopsies are seldom used if CIPN is suspected. Skin biopsy may be beneficial in a patient with a pure sensory presentation who is suspected to have isolated small fiber involvement and when there is benefit in confirming a small fiber neuropathy. In most cases, this is not advised or required.

Although the neuropathies caused by different classes of neurotoxic chemotherapy have many similarities, there are phenotypic differences. The following sections will discuss specific classes of neurotoxic chemotherapies and

KEY POINTS

- **In patients suspected to have chemotherapy-induced peripheral neuropathy by history and examination, the laboratory evaluation for other causes can be simplified to include hemoglobin A_{1C}, vitamin B_{12}, and serum protein electrophoresis with immunofixation. Electrodiagnostic testing is generally not required in these patients.**
- **The most common neurotoxic chemotherapeutic medications that cause chemotherapy-induced peripheral neuropathy are taxanes, platins, vinca alkaloids, and bortezomib.**
- **Taxanes typically cause a sensory-predominant neuropathy that affects both the hands and feet.**

outline their mechanism neuropathy, toxic doses, typical clinical neuropathy phenotypes, and unique phenomena associated with specific drugs.

Taxanes

Taxanes (eg, paclitaxel, docetaxel) are commonly used to treat breast, ovarian, and lung cancers and work by disrupting microtubule function, which is required for cell division. Because of the interference with microtubules, a length-dependent sensory greater than motor neuropathy develops from the disruption of axonal transport, which passes vital proteins and nutrients to the distal reaches of the nerve. It is hypothesized that sensory symptoms predominate as a result of the lack of a blood-nerve barrier at the sensory cell body and, therefore, there is an increased toxicity to sensory as opposed to motor fibers. Generally, neuropathy can begin at a cumulative dose greater than 400 mg/m^2 of docetaxel or 1000 mg/m^2 of paclitaxel, but this varies widely among individual patients.[42]

The neuropathy often affects both the hands and feet. Unique to paclitaxel is paclitaxel-associated acute pain syndrome. Paclitaxel-associated acute pain syndrome consists of myalgias and arthralgias that develop 1 to 7 days after the initiation of paclitaxel and is associated with faster infusion times.[43] Paclitaxel-associated acute pain syndrome typically improves before the next dose of paclitaxel and should not be confused with CIPN, although some experts believe it is associated with the future development of CIPN.

Platins

Platins (ie, cisplatin, carboplatin, oxaliplatin) treat a variety of malignancies, including gynecologic, lung, bladder, gastrointestinal, head and neck, prostate, and testicular cancer. Platins' anticancer mechanism works by cross-linking DNA, resulting in significant errors and triggering cellular apoptosis. Because of the fenestrated capillary network vascularizing the dorsal root ganglion and lack of a blood-nerve barrier, platins concentrate in the dorsal root ganglia and interfere with transcription of neuronal components needed for axonal transport and mitochondrial health.[44,45] Consequently, platinum neuropathy may present similarly to sensory neuronopathy or ganglionopathy, with involvement of the hands and feet, simultaneously. Generally, first-generation platins (oxaliplatin and cisplatin) are associated with more neurotoxicity and higher incidence of CIPN compared with third-generation platins such as carboplatin.[39] Cumulative doses greater than 400 mg/m^2 of cisplatin are associated with CIPN as are a wide range of cumulative doses of oxaliplatin, with reports as low as 110 mg/m^2 of this medication.[46]

Clinically, platinum-associated neuropathy is usually a sensory neuropathy with length dependence, even when the hands and feet are affected at the same time. Platinum-associated neuropathy can continue to worsen after chemotherapy has stopped for approximately 3 months and rarely as much as 6 months.[42] This phenomenon, referred to as "coasting," is likely due to the drugs' ability to concentrate in the mitochondria of the dorsal root ganglion.[47] Interestingly, oxaliplatin can cause painful cold-induced dysesthesias, which often occur in the hours after infusion but then typically self-resolve.

Vinca Alkaloids

Vinca alkaloids (eg, vincristine, vinblastine, vinorelbine) are frequently used to treat leukemia and lymphoma. Vinca alkaloids destabilize the structure of

microtubules and thus interfere with cellular division. Neurotoxic doses are reported at a cumulative total of 30 mg to 50 mg but vary.[46] Similar to taxanes, the disruption of microtubule function affects axonal transport, which is the main mechanism for neuropathy. CIPN due to vinca alkaloids presents with a length-dependent sensorimotor axonal neuropathy, which is often quite painful. Compared with other forms of CIPN, motor involvement is much more common, with upward of 10% of patients having weakness.[39] Autonomic complaints with vinca alkaloids are common, and up to one-third of patients with vinca alkaloid CIPN will report substantial constipation among other symptoms. Although most vinca alkaloid neuropathies present in a subacute length-dependent fashion, infrequent presentations include cranial neuropathy or acute fulminant neuropathies, causing quadriplegia, mimicking GBS.[48,49]

Proteasome Inhibitors

The proteasome inhibitors bortezomib, carfilzomib, and ixazomib are used to treat multiple myeloma and mantle cell lymphoma. The CIPN threshold for bortezomib is normally 25 mg/m^2, which usually occurs around the fifth cycle.[50] The mechanism of neurotoxicity is unknown, but it is thought to be due to toxicity at the dorsal root ganglion with a predilection for small fibers. Therefore, patients present with a painful, mostly length-dependent neuropathy with minimal weakness; however, weakness can be seen in severe cases. A careful history is required in patients with multiple myeloma who are receiving these proteasome inhibitors and present with neuropathy because distinguishing between bortezomib-induced neuropathy and the neuropathy associated with multiple myeloma can be difficult (CASE 7-2).

Other Chemotherapy Agents

Thalidomide, lenalidomide, cytarabine, nelarabine, and epothilones are known to cause CIPN, but they are used less frequently than many of the chemotherapeutics discussed previously. Thalidomide's anticancer effect is by inhibiting tumor necrosis factor α, thereby decreasing angiogenesis. It is used to treat plasma cell dyscrasias such as multiple myeloma. The neuropathy pathogenesis is not fully understood. In addition to causing a length-dependent sensorimotor axonal neuropathy, there is significant autonomic involvement in this setting, with reports of constipation and erectile dysfunction associated with thalidomide.[51] Lenalidomide is an analogue of thalidomide with greater inhibition of tumor necrosis factor α but less neurologic toxicity. Cytarabine and its prodrug, nelarabine, are pyrimidine antagonists used to treat B-cell acute lymphoblastic leukemia and have been associated with acute GBS-like neuropathies that can be accompanied by confusion, headaches, and seizures.[52] Epothilones, such as ixabepilone, have been used to treat metastatic breast cancer resistant to taxane and anthracycline and are associated with a length-dependent, sensory axonal polyneuropathy.[53]

Prevention is an important and evolving topic in CIPN. There are no medications or supplements that have evidence of a protective effect, but there are many agents that ASCO recommends against using.[19] There is no universal consensus for the use of acupuncture, compression, cryotherapy, or exercise for the prevention of CIPN because of multiple studies with conflicting results.[19,54] Several studies have demonstrated exercise could be beneficial for both the prevention of and recovery from CIPN.[54,55] Larger, well-conducted studies are

needed to better understand the effects of cryotherapy because some early studies showed promise, but others did not meet predetermined endpoints.[54]

Treatment of CIPN is supportive, with an emphasis on management of neuropathic pain, treatment of associated conditions, and rehabilitation. It is important to recognize that some patients may defer medications despite the pain because they are tired of using medications, do not want to mask their symptoms, or want to understand whether they are recovering. For the management of neuropathic pain from CIPN, ASCO recommends using

CASE 7-2

A 68-year-old man was referred to the neurology clinic for gait imbalance. He described an unsteady gait but no falls. Further questioning elicited reports of numbness and tightness in his feet, without neuropathic pain. The physical examination showed a mild length-dependent loss of vibration sense and light touch on the feet with preserved strength and reflexes. He was diagnosed with large fiber polyneuropathy, and workup revealed a serum IgM monoclonal gammopathy. Skeletal survey and laboratory workup did not yield evidence of malignancy, diabetes, or vitamin B_{12} deficiency.

He returned to the clinic 2 years later with a recent diagnosis of multiple myeloma and described severe worsening of his neuropathy. With detailed history taking, he recalled very slow mild progression of his neuropathy for 2 years but then a recent onset of excruciating burning pain and progressively worsening balance within 3 months of starting bortezomib. Physical examination revealed additional substantial loss of all sensory modalities and mild distal weakness. The initial differential diagnosis included worsening of his existing neuropathy related to monoclonal gammopathy or multiple myeloma versus bortezomib-related neuropathy. The neuropathy was suspected to be related to bortezomib use because of the temporal relationship between the onset of therapy and symptoms and the dramatic change in the neuropathy phenotype. After a conference call with the patient, oncologist, and neurologist, bortezomib was stopped for a month, and the neuropathy began to improve. Ultimately, the patient was switched to lenalidomide, and he recovered, albeit not entirely from his bortezomib-related neuropathy. His pain was greatly helped by the addition of duloxetine.

COMMENT

This case highlights that the key to chemotherapy-induced peripheral neuropathy diagnosis is often in the history. Detailed clarification of the relationship between symptoms and treatment will often yield a stepwise worsening with each additional chemotherapy treatment and stabilization or improvement with cessation of therapy. Although a monoclonal gammopathy–related neuropathy could worsen as the patient develops multiple myeloma, it would be unusual to have a dramatic change in neuropathy phenotype, particularly as the disease was coming under control with chemotherapy.

duloxetine because it has the best evidence in the CIPN population.[19] Additionally, duloxetine may be a good choice for patients who also have concomitant depression or anxiety or both.[23] After duloxetine, treatment is similar to other painful neuropathies, including tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors (SNRIs), and gabapentinoids. Special attention should be paid to how the side effects of these medications may benefit or harm the patient (TABLE 7-3). Specific dosing recommendations can be found in the guidelines from ASCO or the National Comprehensive Cancer Network.[19] Opiate pain medications seldom work for neuropathic pain in CIPN and can worsen nausea, constipation, and fatigue, all of which are common symptoms among patients with CIPN. It should be emphasized that some patients will have more negative symptoms, such as numbness, instead of positive symptoms, such as tingling and pain, and these patients with negative symptoms likely will not need neuropathic pain medications but rather education and functional evaluation. Patients with CIPN are at an increased risk of falls and fractures; therefore, any concerns about functional mobility should prompt a referral to a physical medicine and rehabilitation specialist or physical therapist for comprehensive fall-risk reduction.[22,24,25] In the absence of a referral to a rehabilitation expert, a gait aid, such as a walking stick or a cane, may be beneficial. Similarly, difficulty with activities of daily living, such as feeding or

Neuropathic Pain Medication for Chemotherapy-induced Peripheral Neuropathy TABLE 7-3

Agent	Class	Typical dosage	Side effects	Contraindications
Duloxetine[a]	Serotonin norepinephrine reuptake inhibitor (SNRI)	30-60 mg daily	Abdominal discomfort, sleepiness, dry mouth, hypertension, hyperhidrosis	Current use of tamoxifen, caution with concomitant serotonergic agents
Gabapentin	Gabapentinoid	300-3600 mg/d[b]	Sleepiness, brain fog, edema	Renal failure, renal impairment requires dose adjustment
Pregabalin	Gabapentinoid	300-600 mg/d[b]	Sleepiness, brain fog, edema	Same as gabapentin
Mexiletine	Antiarrhythmic	300-450 mg/d[b]	Gastroesophageal reflux	QRS prolongation, cardiac arrhythmia
Nortriptyline or amitriptyline	Tricyclic antidepressant	25-100 mg every night at bedtime	Dry mouth, sleepiness	Corrected QT interval prolongation, caution with concomitant serotonergic agents
Topical gel Baclofen-amitriptyline-ketamine	Multiple classes	Applied 1-4 times per day	Skin irritation	Open cuts or wounds
Lidocaine	Antiarrhythmic and anesthetic	Applied 1-4 times per day	Skin irritation	Open cuts or wounds

[a] Recommended by the American Society of Clinical Oncology.
[b] Typically split over 3 doses and based on renal function.

dressing, and difficulty with fine motor movements can be addressed with modifications, equipment, and exercises from an occupational therapist. Specific rehabilitation programs, modalities, and alternative therapies lack evidence to support their use; however, ongoing randomized controlled trials are evaluating the efficacy of tai chi and acupuncture.[26-28]

The prognosis of patients with CIPN depends on both the severity of the neuropathy as well as the plan for any additional neurotoxic chemotherapy. The natural history of recovery from CIPN is not well understood, but generally, improvement in sensory and motor function occurs in a proximal to distal gradient over 2 years. Most patients recover substantially, but recovery can be incomplete.[25,56] Although the rate of long-term CIPN varies widely, many CIPN survivors continue to have difficulty with pain, proprioception, mobility, activities of daily living, and falls.[22,25,57,58] Overall, CIPN is an underrecognized toxic neuropathy that occurs with neurotoxic chemotherapy in which proper management can greatly improve the function and quality of life of cancer survivors.

KEY POINTS

- Duloxetine has the most supporting evidence for the treatment of neuropathic pain in chemotherapy-induced peripheral neuropathy.
- Chemotherapy-induced peripheral neuropathy management should be multidisciplinary, focusing on pain management, rehabilitation, and quality of life because there are no current disease-modifying therapies, and many cancer survivors will have a normal lifespan.
- Chloroquine can cause a vacuolar myopathy and sensorimotor polyneuropathy with some demyelinating features.

Non–Cancer-therapy-related Toxic Neuropathies

Many classes of nonchemotherapeutic medications can cause neuropathy, although these are collectively uncommon. It is useful to think about these medications by either drug class or use, as categorized in TABLE 7-4. The following sections will highlight some of the neuropathies associated with these medications that are of particular importance. The first-line treatment for nearly all these toxic neuropathies is a cessation of the causative agent. The literature on prognosis is very limited, but generally, improvement in the neuropathy is expected over the course of weeks to months.

Immunosuppressants

Immunosuppressive medications historically used to treat rheumatologic diseases can cause drug-induced or toxic neuropathies.

COLCHICINE. Colchicine is used to treat gout and pericarditis and interferes with microtubule assembly. Colchicine has been associated with a rare toxic sensorimotor axonal neuropathy in patients with concomitant end-stage renal disease.[59] These patients can have myopathic and mild neurogenic findings (neuromyopathy) on electrodiagnostic studies.[60] It is believed that the renal impairment confers the neuromuscular toxicity of colchicine and the neuropathy improves with the discontinuation of colchicine.

CHLOROQUINE AND HYDROXYCHLOROQUINE. Chloroquine and its hydroxylated analogue, hydroxychloroquine, were originally developed as antiparasitic medications used for malaria, but they are now commonly used to treat autoimmune diseases, such as lupus, and recently drew interest as an unvalidated treatment for COVID-19. Chloroquine inhibits lysosomal enzymes within glycogen and protein metabolic pathways, causing chronic neuromyopathy. The myopathy is classically vacuolar, whereas the sensorimotor neuropathy typically has mixed demyelinating and axonal features.[61] Risk factors for developing toxicity include older age, doses greater than 5 mg/kg ideal body weight, and duration of more than 5 years.[61] Any sign of toxicity should prompt cessation of therapy and ophthalmic screening for retinopathy, which can be irreversible.

TACROLIMUS. Tacrolimus is a calcineurin inhibitor that alters interleukin-2 production and ultimately suppresses T-cell activity. Tacrolimus is primarily used in organ transplantation.[62] Tacrolimus toxicity can cause neuropathy, often accompanied by a tremor, headache, and occasionally seizures.[63] The mechanism of toxicity is thought to be decreasing calcineurin's role in modulating Na^+/K^+ ATPase activity. Estimates vary widely, but up to 40% of patients treated with tacrolimus develop a chronic multifocal demyelinating neuropathy.[64] Risk factors for tacrolimus neurotoxicity include peak blood serum levels of the drug, liver failure, and specific polymorphisms in the *MDR1* gene.[63] There are reports of patients improving after cessation of tacrolimus and treatment with IVIg.[65]

Medications Associated With Neuropathies, Grouped by Drug Class TABLE 7-4

Class and subclass	Medication
Immune checkpoint inhibitors	
Cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody	Ipilimumab, tremelimumab
Programmed cell death protein-1 monoclonal antibody	Nivolumab, pembrolizumab, pidilizumab, cemiplimab
Ligand of PD-1 monoclonal antibody	Atezolizumab, durvalumab, avelumab
Chemotherapy	
Taxane	Paclitaxel, docetaxel, cabazitaxel
Platin	Carboplatinum, cisplatinum, oxaliplatinum
Vinca alkaloids	Vincristine, vinblastine
Proteosome inhibitor	Bortezomib, ixazomib, carfilzomib
TNF-α antagonist and antiangiogenic medication	Thalidomide, lenalidomide
Nucleoside analogue and antimetabolite	Cytarabine, nelarabine
Epothilone	Ixabepilone
Immunosuppressive and antirheumatic	Colchicine, gold, chloroquine, tacrolimus, etanercept, cyclosporine, allopurinol, sulfasalazine, infliximab
Cardiovascular	Amiodarone, hydralazine, perhexiline, statins, propafenone
Antimicrobial	Isoniazid, metronidazole, nitrofurantoin, nucleoside analogues, fluoroquinolones, chloramphenicol, dapsone, ethambutol, linezolid, D-penicillamine
Other	Phenytoin, nitrous oxide, pyridoxine
Recreational	Alcohol, n-hexane

KEY POINTS

- A study published in 2022 suggests that statin-induced neuropathy is much less common than previously thought.

- Diabetes or prediabetes, vitamin deficiency, and alcohol misuse remain the most common identifiable causes of neuropathy in the United States.

- The primary mechanism of neuropathy associated with long-term use of high doses of isoniazid is related to vitamin B_6 deficiency.

Cardiovascular Medications

Neuropathy as a side effect of cardiovascular medications can be challenging to recognize if there are coexistent comorbidities such as diabetes, hypercholesterolemia, or metabolic syndrome, which can cause neuropathy.

AMIODARONE. Amiodarone is an antiarrhythmic medication that is used in acute cardiac arrest, ventricular tachycardia, as well atrial fibrillation. Amiodarone targets voltage-gated potassium and calcium channels. High doses (greater than 400 mg/d) and prolonged administration (greater than 1 year) can cause neurotoxicity. Although rare, neurotoxicity presents with tremors, cognitive impairment, optic neuropathy, peripheral neuropathy, and very rarely myopathy. Clinically, a toxic neuropathy from amiodarone is a chronic, length-dependent sensorimotor axonal neuropathy.[66]

HYDRALAZINE. Hydralazine is prescribed for the management of hypertension, and it acts by increasing calcium levels to cause vasodilation. Neuropathy is thought to develop because of excess urinary excretion of vitamin B_6 (pyridoxine), causing a relative deficiency in vitamin B_6. It presents as a length-dependent, sensory greater than motor, axonal polyneuropathy.[67] Overall, hydralazine-related neuropathy is rare, but because of this medication's relatively common use as an antihypertensive, it should be considered in the appropriate setting.

STATINS. Statins are one of the most prescribed medication classes worldwide, and historically they have been associated with a chronic length-dependent sensory greater than motor axonal polyneuropathy. Statin use was frequently considered among the differential diagnoses for otherwise idiopathic neuropathies until a large meta-analysis, published in 2022, involving diabetic and nondiabetic populations demonstrated there was no increased risk of peripheral neuropathy with statin use.[68] Given this new information, statin-induced neuropathy is likely rare and should be a diagnosis of exclusion because of the low incidence despite wide application.[68] It is important to point out that the various muscle toxicities associated with statins, ranging from myalgia, which is common, to necrotizing myopathy, which is rare, should always be considered in patients taking statins who report myopathic symptoms. See CASE 7-3 for an example.

Antimicrobials and Antivirals

There are a variety of antimicrobial and antiviral agents that are associated with toxic neuropathies. The broader list is included in TABLE 7-4, but selected agents are reviewed in the following sections.

ISONIAZID. Isoniazid is regularly used in the treatment of tuberculosis. It works by disrupting cell wall synthesis. Isoniazid-associated neuropathy presents as a chronic length-dependent sensory large fiber axonal neuropathy. The mechanism of neuropathy is believed to be secondary to vitamin B_6 deficiency that is caused by long-term use and high doses of isoniazid, such as dosages used in the treatment of tuberculous meningitis. Additionally, polymorphisms in the gene responsible for acetylation of isoniazid may place some individuals at higher risk for neuropathy.[70] For prevention, individuals on isoniazid therapy should be

placed on pyridoxine prophylaxis, but practitioners should avoid oversupplementation as this can cause pyridoxine toxicity.

METRONIDAZOLE. Metronidazole is a commonly used antibiotic for anaerobic bacterial infections and has been associated with length-dependent large fiber sensory axonal neuropathy.[71] The exact neurotoxic dose is not known; however, in a recent case series, 31 of 40 cases occurred with doses of more than 42 g total or a course of greater than or equal to 4 weeks. These doses are sometimes seen in the treatment of *Helicobacter pylori* and infections associated with Crohn disease.[71] The pathophysiology of metronidazole neuropathy is not well understood, but the prognosis is good, with most patients reporting significant improvement after the cessation of metronidazole.

NUCLEOSIDE ANALOGUES (ANTIRETROVIRALS). Nucleoside analogues or antiretroviral medications are regularly used to treat and prevent HIV and acquired

CASE 7-3

A 58-year-old woman was referred to a neurology department for evaluation of suspected statin-induced neuropathy. The patient was slightly overweight and had a 5-year history of hyperlipidemia. She described 16 months of slowly progressive numbness that began at the tips of her toes and eventually progressed to the base of her toes. She described this sensation as a “bunched-up sock” with pins and needles. She had no upper-extremity symptoms and no weakness or gait instability. She had not taken any neuropathic pain medications, but she described that the symptoms bothered her less after her one or two martinis, which had been her nightly routine for the past 10 years. Statin therapy with simvastatin was initiated 3 years before her visit. The primary care physician stopped the simvastatin 3 months before her visit because of suspected statin neuropathy, but her symptoms remained unchanged. Physical examination showed reduced pinprick and temperature sensation on her toes and distal feet bilaterally, slightly reduced vibratory sense, and reduced Achilles reflexes with preserved strength. Laboratory testing revealed a hemoglobin A_{1c} level of 5.5 g/dL, continued hyperlipidemia with normal vitamin B_1, B_6, and B_{12} levels, and normal blood serum protein electrophoresis results. Given the duration, consistency, and volume of her alcohol consumption, her neuropathy was deemed attributable to alcohol. Statin-related neuropathy was much less likely because it is very uncommon, and her symptoms did not improve with medication cessation.

COMMENT

Diabetes or prediabetes, vitamin deficiency, and alcohol misuse remain the most common identifiable causes of neuropathy in the United States.[69] It is important to remember that alcohol-related neuropathy can occur in the absence of vitamin deficiency and malnutrition, although the three are often hard to separate.

KEY POINTS

- It can be challenging to differentiate human immunodeficiency virus (HIV) neuropathy from neuropathy caused by antiretroviral drugs, and the diagnosis can be aided by looking for other signs of toxicity.

- A comprehensive social and occupational history is important when heavy metal neuropathy is suspected.

immunodeficiency syndrome (AIDS) as they inhibit reverse transcriptase, preventing viral replication. Older antiretroviral drugs such as stavudine, didanosine, and zalcitabine have the strongest association with a subacute length-dependent sensory greater than motor axonal neuropathy.[72,73] It is often difficult to distinguish between HIV neuropathy and antiretroviral therapy-related neuropathy; however, signs of systemic antiretroviral therapy toxicity, including elevated lactate levels, lipodystrophy, and myopathy, can help differentiate the two diagnoses. In these cases, it is important to look for other signs of toxicity. The incidence of neuropathy with newer antiretroviral agents, such as tenofovir, is lower, but they can cause painful length-dependent sensory neuropathy.[74]

FLUOROQUINOLONES. Fluoroquinolones can cause length-dependent symmetric peripheral neuropathy, although there is disagreement in the literature about how frequently this occurs. A 2019 study showed a particular predilection for this neuropathy in men older than 60 years.[75] As most of the reports of fluoroquinolone neuropathy are found in health care claims research, the particular phenotype is not well described. Fluoroquinolones are associated with a host of drug toxicities, some of which are musculoskeletal, which can sometimes complicate the diagnosis. Patients with substantial pain should be screened for tendon rupture or tendinopathy because this is well described. Overall, more research is required to strengthen the association of a medication-induced neuropathy with fluoroquinolones.

Antiseizure Medications

Phenytoin is an antiseizure medication associated with length-dependent sensory axonal peripheral neuropathy in the setting of long-term high doses. Phenytoin can have other toxicities, specifically gingival hyperplasia, ataxia, and rare reports of inflammatory myopathy. Because of a lack of large prospective studies and a reliance on case reports, the exact mechanism of neural injury by phenytoin remains unclear.[76]

Heavy Metals

Heavy metals are well known to cause various toxic neuropathies. Although the overall incidence has decreased over time with increasing awareness and changes in occupational and environmental exposures, it is important to know the clinical syndromes and screen for them when appropriate. A summary of heavy metal neuropathies discussed is included in **TABLE 7-5**.

LEAD. Lead exposure can occur with wet paint, paint chips, distillation of alcohol, smelting, herbal or natural medicines, and contaminated drinking water. Based on the body surface exposed, the duration of contact, and the dose, the neuropathy can be acute, often with profound motor involvement manifesting as weakness, with a predilection for the radial nerve, causing wrist drop. With long-term exposure and exposure to lower levels, the resulting neuropathy is more length-dependent, affecting the axons of both sensory and motor fibers.[77] Chronic lead toxicity and neuropathy may be accompanied by lead lines in the gums, cognitive dysfunction, abdominal pain, and hypertension.[78,79] Lead toxicity is best evaluated with blood serum level tests and, depending on levels, management may range from exposure reduction to chelation therapies.[80]

MERCURY. The phenotype of neuropathy from mercury exposure depends on the type of exposure. Short-term exposure can lead to a motor axonal neuropathy, whereas long-term exposure tends to cause a sensory greater than motor, length-dependent axonal neuropathy. Exposure to liquid mercury or vapor can occur with occupational exposure with hatting, thermometer or fluorescent light manufacturing, mining, and dental amalgams.[81,82] Mercury poisoning can have significant neurologic toxicity with encephalopathy, psychosis, and ataxia, in addition to renal impairment and rarely with acrodynia, in which the skin becomes pink and peels (FIGURE 7-3[79,83]).[84,85] Management of mercury toxicity depends on both the severity of the symptoms and mercury level exposure and ranges from exposure reduction to chelation therapies.[86]

ARSENIC. Arsenic neuropathy, although not common, can be both serious and associated with attempts at intentional poisoning. Arsenic exposure can also be the result of mining, alternative medicines, and drinking contaminated water.[87] Clinically, it manifests as a distal large fiber axonal neuropathy and can be accompanied by skin changes, including horizontal lines on nail beds (Mees lines [FIGURE 7-3]), malaise, nausea, vomiting, and renal impairment.[83,88,89] Arsenic levels are measured through urinalysis if toxicity is acute and hair analysis if toxicity is chronic. Management is determined based on the degree of

Heavy Metals Associated With Neuropathy

TABLE 7-5

Metal	Characteristics of neuropathy	Sources of exposure	Non-neuropathic signs and sequelae	Diagnostic tests
Lead	Acute: predilection for motor fibers Chronic: distal sensorimotor axonal peripheral neuropathy	Wet and dry paint, soil, alcohol, drinking water	Lead lines on the gums of the oral pharynx, basophilic stippling on red blood cells, cognitive dysfunction, hypertension	Serum level, bone level
Mercury	Acute: motor neuropathy Chronic: distal sensory greater than motor axonal neuropathy	Hat, thermometer, or fluorescent light manufacturing, mining, dental amalgams	Encephalopathy, psychosis, ataxia, renal impairment, and rarely acrodynia	Serum levels or 24-hour urine levels
Arsenic	Distal large fiber axonal neuropathy	Poisoning, mining, alternative medicines, drinking water	Gastrointestinal effects, malaise, anorexia, renal impairment, skin hyperkeratosis, Mees lines	Acute: 24-hour urine levels Chronic: hair levels
Zinc toxicity and copper deficiency	Myeloneuropathy with sensorimotor axon loss	Denture cream, supplements, ingested coins	ECG abnormalities, neutropenia, anemia, myelodysplastic syndrome	Serum: zinc, copper, ceruloplasmin Urine: 24-hour levels of copper and zinc

ECG = electrocardiogram.

FIGURE 7-3
Examination findings from heavy metal toxicity. *A*, Mees lines in arsenic toxicity, a dark horizontal line on the nail bed (*arrow*). B, Lead lines in lead toxicity, dark lines around gum lines (*arrow*). *C*, Acrodynia (pink disease) from mercury toxicity demonstrating the pink coloring of the feet.
Panel A reprinted with permission from Sharma S, et al.[83] © 2016 The Authors. Published by Oxford University Press on behalf of the Association of Physicians. Panel B reprinted with permission from Helmich F, Lock G, N Engl J Med. © 2018 Massachusetts Medical Society.[79] Panel C reprinted with permission from Weinstein M, Bernstein S, CMAJ.[84] © 2003 Canadian Medical Association.

involvement and measured levels, with chelation therapy being reserved for significantly elevated levels of arsenic.

ZINC TOXICITY AND COPPER DEFICIENCY. Zinc toxicity can result in a myeloneuropathy by impairing copper absorption. Clinically, this manifests with significant gait ataxia from a combination of dorsal column degeneration and sensory and motor axonal loss.[90] Long-term zinc exposure has been reported from the use of zinc supplements and denture creams as well as contact with coins.[91] Zinc toxicity should be considered in the differential diagnosis for myeloneuropathy and other presenting sequela of copper deficiency, such as optic neuropathy, anemia, and neutropenia. Diagnostic testing for suspected copper deficiency should include testing for zinc with serum levels and copper deficiency with serum and urine levels. In the setting of zinc toxicity, the mechanism of exposure should be identified and eradicated in concert with appropriate copper supplementation. For more information about nutritional neuropathy, refer to the article “Nutritional Neuropathies” by Neeraj Kumar, MD,[92] in this issue of *Continuum*.

Overall, toxic neuropathies from heavy metals are important to detect and manage with a reduction in exposure and proper clinical interventions.

CONCLUSION

Although most neuropathies seen in clinical practice are either diabetic or idiopathic, it is vitally important to recognize toxic neuropathies when they occur. A thorough understanding of their distinctive clinical presentations and risk factors will aid in recognition. In contrast to many other forms of neuropathy, most toxic neuropathies improve with the correct treatment. Further research is needed to better understand the pathophysiology of the most common forms, including those from chemotherapy, to facilitate the development of effective preventive and treatment strategies.

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Nutritional Neuropathies

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

By Neeraj Kumar, MD

ABSTRACT

OBJECTIVE: This article reviews the etiologies, presentations, and management of neuropathies related to nutritional deficiencies.

LATEST DEVELOPMENTS: Peripheral neuropathy can be the predominant or only manifestation of certain nutrient deficiencies. Cognitive difficulties or involvement of other parts of the central nervous system, such as the optic nerve and spinal cord, may accompany nutritional peripheral neuropathies. In most patients, the nutritional deficiency may have a single predominant cause, but in some cases, multiple causes may coexist. Obesity, for unclear reasons, can be associated with nutrient deficiencies. The rising rates of bariatric surgery and the incidence of nutrient deficiencies following bariatric surgery make this a particularly relevant topic for neurologists.

ESSENTIAL POINTS: Neuropathies caused by nutrient deficiencies are preventable with appropriate supplementation in high-risk situations. Early recognition and prompt treatment are essential to ensure an optimal outcome and minimize neurologic morbidity.

INTRODUCTION

The health of the peripheral nervous system depends on an adequate supply of essential nutrients. This article reviews the clinical features, evaluation, and management of peripheral nerve disorders associated with nutritional disorders, most frequently nutrient deficiencies. The tables in this article provide a summary of some of the key nutrients that cause neuropathies (reference daily intake, major nutrient sources, major causes of the deficiency, neurologic significance, laboratory tests, and management of deficiency causes). The reference daily intake noted in the tables is obtained from the US Food and Drug Administration (FDA) website.[1] This article includes landmark and recent references and directs the reader to review articles for detailed bibliographies.[2-7] Normal values, when reported in this article, are accompanied by the caveat that the values vary among different laboratories and methods used. The dose, route, and duration of replacement therapy with nutritional deficiencies are often empiric and dictated by anecdotal observations and responses to therapy rather than based on rigorous studies.

NUTRIENT METABOLISM AND NEUROLOGIC HEALTH

The B-group vitamins are particularly important in neurologic function. Of the B-group vitamins, those whose deficiency is associated with neurologic disease include vitamin B_1 (thiamine), vitamin B_3 (niacin), vitamin B_6 (pyridoxine),

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Address correspondence to Dr Neeraj Kumar, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, kumar.neeraj@mayo.edu.

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vitamin B_9 (folate), and vitamin B_{12} (cobalamin).[8,9] Vitamin B_6 toxicity can cause a sensory neuronopathy. Other important vitamins for optimal nervous system function include vitamin D and vitamin E. Vitamin D deficiency is seen in many diseases, most notably multiple sclerosis. However, the precise significance of this association remains a matter of debate. Myopathy is perhaps the most characteristic neurologic manifestation of vitamin D deficiency. Vitamin A toxicity has been implicated in pseudotumor cerebri. Vitamin A deficiency causes impaired vision (night blindness).

Although vitamin B_5 (pantothenic acid) and vitamin B_7 (biotin) are essential for nervous system function, their clinical relevance primarily relates to inherited conditions such as pantothenate kinase-associated neurodegeneration, characterized by basal ganglia iron accumulation and biotinidase deficiency, resulting in optic neuropathy and myelopathy. Vitamin E, thiamine, riboflavin, pyridoxine, biotin, folic acid, and cobalamin are also implicated in rare genetic disorders with childhood-onset presentations, which differ significantly from the adult-onset presentations related to these vitamin deficiencies. The underlying pathophysiology in many of these disorders involves transporter proteins and not nutritional factors. These conditions are therefore not reviewed in this article. Although some patients with these disorders may have neuropathy, it is generally not the predominant manifestation.

Essential minerals include sodium, potassium, calcium, magnesium, chloride, phosphorus, iodine, iron, copper, zinc, manganese, sulfur, and selenium. From the perspective of nutritional neuropathy, copper deficiency is the only relevant mineral deficiency discussed in this article.

Often multiple nutrient deficiencies coexist, both the central and peripheral nervous systems can be involved, and multiple causes of these deficiencies can be present. Therefore, patients with a neurologic manifestation related to a particular nutrient deficiency need a comprehensive evaluation to identify other nutrient deficiencies, look for subclinical disease in other parts of the nervous system, and identify the cause or causes of the deficiency state. Copper and vitamin B_{12} deficiencies can coexist after bariatric surgery. Copper deficiency may be caused by reduced absorption following bariatric surgery and by the prolonged use of oral zinc supplements. Vitamin B_{12}, folate, vitamin E, and copper deficiencies often have spinal cord involvement associated with neuropathy. Although thiamine deficiency can result in acute and chronic neuropathy, central nervous system manifestations (Wernicke-Korsakoff syndrome) are a hallmark of thiamine deficiency. Hematologic abnormalities often accompany vitamin B_{12}, folate, and copper deficiency. Skin or mucous membrane abnormalities are an important systemic manifestation of many B-group vitamin deficiencies. Although this article focuses on nutritional neuropathies, it is important to recognize the systemic or central nervous system manifestations because these often aid in the diagnosis. Nutritional neuropathies are generally axonal; the presence of a predominantly demyelinating neuropathy should prompt a search for alternative etiologies.

Neurologic involvement is generally a late manifestation of malnutrition except for manifestations caused by thiamine and folate deficiency. Early recognition and prompt treatment are important to minimize neurologic morbidity and mortality. Timely repletion can stabilize or reverse deficits.

Individuals at risk for nutritional deficiencies include those who have malabsorption in the context of diseases such as pernicious anemia,

inflammatory bowel disease, celiac disease, Whipple disease, intestinal infections and infestations, cystic fibrosis, tropical sprue, and bacterial overgrowth. Gastrointestinal surgeries, particularly bariatric surgery and intestinal resections may be associated with vitamin and mineral deficiencies. Liver and pancreatic disease are additional causes of malabsorption. Prior abdominal radiation is an iatrogenic cause of malabsorption. People whose incomes are below the federal poverty threshold, people experiencing homelessness, older adults, pregnant patients, and individuals with cognitive impairment are at particular risk, as are those who adhere to food fads or have eating disorders such as bulimia or anorexia nervosa and individuals on prolonged or inadequately supplemented parenteral nutrition. Alcohol use disorder can be associated with neurologic manifestation caused by nutrient deficiency or direct neurotoxicity caused by alcohol use. Nutrient deficiencies are seen not only with malnutrition but also with obesity.

NUTRIENT DEFICIENCIES

This section summarizes the common causes of specific nutrient deficiencies, the resulting neurologic manifestations, and management of the deficiency state.

Vitamin B_{12}

This section discusses the causes, neurologic manifestations, and treatment of vitamin B_{12} deficiency (TABLE 8-1).

BACKGROUND. The terms *B_{12}*, *vitamin B_{12}*, *cobalamin*, and *cyanocobalamin* are often used interchangeably. Vitamin B_{12} is a water-soluble vitamin that acts as a cofactor in methylation reactions. The active coenzyme forms are methylcobalamin and adenosylcobalamin.[10,11] Methylcobalamin is a cofactor for methionine synthase that converts homocysteine to methionine. Methionine is adenosylated to *S*-adenosyl methionine, which is a methyl group donor and is responsible for neuronal methylation reactions such as the methylation of myelin basic protein. Adenosylcobalamin is a cofactor for mitochondrial L-methylmalonyl coenzyme A mutase, which converts L-methylmalonyl coenzyme A to succinyl coenzyme A. Impairment of this reaction results in the accumulation of methylmalonate and propionate, which provide abnormal substrates for fatty acid synthesis. The primary dietary sources of vitamin B_{12} are meat, fish, and dairy.

DEFICIENCY CAUSES. Pernicious anemia is most commonly seen in older adults, but any age group can be affected.[12,13] In pernicious anemia, an immune-mediated destruction of gastric parietal cells occurs, which results in a lack of intrinsic factor required for the binding and subsequent transfer of ingested vitamin B_{12} to the distal ileum for absorption. Additionally, patients with pernicious anemia may have anti-intrinsic factor and antiparietal cell antibodies. An immune response directed against the gastric hydrogen-potassium ATPase accounts for the associated achlorhydria. Pernicious anemia may be accompanied by iron deficiency, increased risk of gastric cancer or carcinoid, and other autoimmune diseases such as autoimmune thyroiditis, Addison disease, vitiligo, and type 1 diabetes.

Because an acidic environment in the stomach is essential for releasing food-bound vitamin B_{12}, conditions that cause hypochlorhydria (eg, using

KEY POINTS

- The B-group vitamins whose deficiency is associated with neurologic disease include vitamin B_1 (thiamine), vitamin B_3 (niacin), vitamin B_6 (pyridoxine), vitamin B_9 (folic acid), and vitamin B_{12} (cobalamin).

- When multiple nutrient deficiencies coexist, both the central and peripheral nervous systems can be involved, and multiple causes of these deficiencies can be present.

- Vitamin B_{12}, folate, vitamin E, and copper deficiencies often have associated spinal cord involvement along with peripheral neuropathy.

- Except for manifestations caused by thiamine and folate deficiency, neurologic manifestations are generally seen in the late stages of malnutrition.

- Pernicious anemia may be accompanied by iron deficiency, increased risk of gastric cancer or carcinoid, and other autoimmune diseases such as autoimmune thyroiditis, Addison disease, vitiligo, and type 1 diabetes.

antacids or proton-pump inhibitors, gastritis, and gastrectomy) can result in vitamin B_{12} deficiency. Food-bound vitamin B_{12} malabsorption is particularly common in older adults because of the high incidence of atrophic gastritis; however, this is often unaccompanied by clinical manifestations, and the precise significance of subclinical vitamin B_{12} deficiency and its management is poorly understood.[14,15] Vegetarians have a higher incidence of vitamin B_{12} deficiency, but this is usually subclinical. Vitamin B_{12} secreted in the bile is reabsorbed along with vitamin B_{12} derived from sloughed intestinal cells. Therefore, vitamin B_{12} deficiency is not universal in those who do not eat any animal products. However, in the setting of an additional cause of vitamin B_{12} deficiency, vegetarians may develop symptomatic vitamin B_{12} deficiency more rapidly. Although metformin can lower vitamin B_{12} levels, the clinical significance of this is unclear. Typically, it takes 4 to 5 years of malabsorption to develop clinically significant vitamin B_{12} deficiency because of large hepatic stores and minute daily losses. Gastrointestinal diseases, particularly those that involve the stomach or distal ileum, can result in vitamin B_{12} deficiency. Pancreatic proteases are required to release vitamin B_{12} bound to haptocorrin, a B_{12} binding glycoprotein secreted by the salivary and gastric glands, before vitamin B_{12} can bind to

TABLE 8-1 **Vitamin B_{12} (Cobalamin) Deficiency**

Reference daily intake: 2.4 µg

Major dietary sources

- Meat, poultry, fish, eggs, dairy products, fortified soymilk, cereals

Deficiency causes

- Pernicious anemia, advanced age (atrophic gastritis), vegan and vegetarian diets, poor nutrition (as with alcohol use disorder), gastrointestinal surgery (gastrectomy, bariatric surgery, ileocecal resection), acid reduction therapy, gastrointestinal disease (Crohn disease, celiac disease), pancreatic disease, nitrous oxide toxicity

Neurologic manifestations

- Peripheral neuropathy, myelopathy, myeloneuropathy, neuropsychiatric manifestations, optic neuropathy, autonomic dysfunction

Laboratory tests

- Serum vitamin B_{12}, serum methylmalonic acid, plasma homocysteine, serum holotranscobalamin, complete cell count (hemoglobin, mean corpuscular volume, peripheral smear), serum gastrin, intrinsic factor antibodies, parietal cell antibodies, tests for associated conditions (iron profile, upper endoscopy, thyroid disease, Addison disease); rule out coexisting nutrient deficiencies (particularly folate and copper)

Management

- 1000 µg IM vitamin B_{12} given daily for 5 days, weekly for a month, and monthly thereafter

Additional comments

- Many years may elapse before the body's vitamin B_{12} stores are depleted enough to cause clinical vitamin B_{12} deficiency
- Neurologic manifestations may be unaccompanied by hematologic derangement

IM = intramuscular.

intrinsic factor; therefore, pancreatic disease can also result in vitamin B_{12} deficiency. Nitrous oxide (laughing gas) may be abused in the form of "whippets." Nitrous oxide oxidizes the cobalt core of cobalamin and renders cobalamin inactive. In this setting, although low or low-normal vitamin B_{12} levels may be present, the pathophysiologic hallmark is a functionally inactive vitamin B_{12}, leading to a syndrome typical of vitamin B_{12} deficiency.

NEUROLOGIC MANIFESTATIONS. The classic neurologic manifestation of vitamin B_{12} deficiency is the subacute combined degeneration of the spinal cord. Peripheral neuropathy may coexist or be independently present. Concomitant onset of hand and foot paresthesia, disproportionate and severe dorsal column dysfunction, brisk knee jerks with reduced ankle reflexes, and Lhermitte signs all indicate myelopathy accompanying the neuropathy.[16] The neuropathy is typically a sensory-predominant axonal neuropathy, although a pure sensory neuropathy (large or small fiber) and autonomic dysfunction have all been described. Vitamin B_{12} deficiency can result in neuropsychiatric manifestations such as depression, cognitive impairment, and psychosis, but these have been poorly characterized. Because low vitamin B_{12} levels are commonly seen in older adults, the specific cause and effect can be hard to establish in patients with peripheral neuropathy or memory impairment. The presence of other biochemical biomarkers for a metabolically significant vitamin B_{12} deficiency (elevated methylmalonic acid and homocysteine), the presence of a cause for vitamin B_{12} deficiency, and associated hematologic manifestations caused by vitamin B_{12} deficiency (megaloblastic anemia, macrocytosis, hypersegmented polymorphonuclear cells) can help establish an association between the laboratory finding and clinical context. Neurologic manifestations of vitamin B_{12} deficiency are often unaccompanied by hematologic derangement.

INVESTIGATIONS AND MANAGEMENT. Although serum B_{12} measurement is a widely used screening test, it has technical and interpretive problems and lacks sensitivity and specificity for diagnosing vitamin B_{12} deficiency.[17] Holotranscobalamin (transcobalamin-bound cobalamin) represents the metabolically active vitamin B_{12}, and its measurement can be particularly useful in equivocal cases; however, the test has limited worldwide availability. The range of normal serum vitamin B_{12} is rather broad: 180 ng/L to 914 ng/L, with levels between 150 ng/L and 399 ng/L considered borderline. The presence of elevated methylmalonic acid and homocysteine levels are important indications for metabolically significant vitamin B_{12} deficiency; the former is more specific than the latter because homocysteine can also be elevated in folate deficiency. Health care providers should obtain a baseline methylmalonic acid level to monitor a patient's response to treatment. Tests to identify underlying pernicious anemia could include serum gastrin, pepsinogen I, antiparietal cell antibodies, and anti-intrinsic factor antibodies. Elevated serum gastrin and decreased serum pepsinogen I are common in pernicious anemia. A lack of serum gastrin elevation should bring into question the diagnosis of pernicious anemia. Anti-intrinsic factor antibodies are specific but not extremely sensitive. Antiparietal cell antibodies are nonspecific and can also be elevated in 10% of individuals over 70 years of age. The Schilling test is no longer used because it was plagued by technical and interpretive problems. A common approach to diagnosing pernicious anemia is combining the specific but

KEY POINTS

- **Food-bound vitamin B_{12} malabsorption is particularly common in older adults because of the high incidence of atrophic gastritis; however, this is often unaccompanied by clinical manifestations, and the precise significance of subclinical vitamin B_{12} deficiency and its management is poorly understood.**

- **Typically, it takes 4 to 5 years of malabsorption to develop clinically apparent vitamin B_{12} deficiency because of large hepatic stores and minute daily losses.**

- **Nitrous oxide oxidizes the cobalt core of cobalamin and renders cobalamin inactive. In this setting, although low or low-normal vitamin B_{12} levels may be present, the pathophysiologic hallmark is a functionally inactive vitamin B_{12}, leading to a syndrome typical of vitamin B_{12} deficiency.**

- **The classic neurologic manifestation of vitamin B_{12} deficiency is a subacute combined degeneration of the spinal cord. Peripheral neuropathy may coexist or be independently present.**

- **Concomitant onset of hand and foot paresthesia, disproportionate and severe dorsal column dysfunction, brisk knee jerks with reduced ankle reflexes, and Lhermitte signs indicate a myelopathy accompanying the neuropathy of vitamin B_{12} deficiency.**

insensitive intrinsic factor antibody test with the sensitive but nonspecific serum gastrin level test.

Particularly in the presence of prominent neurologic manifestations, parenteral vitamin B_{12} replacement therapy is generally preferred over oral therapy because of concerns regarding a slower response with oral therapy.[18] While a high enough oral dose (1000 µg/d to 2000 µg/d) may lead to adequate vitamin B_{12} absorption, oral therapy is generally reserved for patients with no neurologic manifestations or for maintenance after the initial response to parenteral therapy in those with neurologic manifestations. The neurologic response is slower and less predictable than the response of hematologic derangements.

Folic Acid

This section discusses the causes of folic acid deficiency, the neurologic manifestations of folic acid deficiency, and the management of the deficiency state (TABLE 8-2).

BACKGROUND. The term *folate* typically includes both the naturally occurring form of vitamin B_9 (folate) and the synthetic form (folic acid). The primary biologically active forms of folate are dihydrofolate and tetrahydrofolate.[19]

TABLE 8-2

Folate (Vitamin B_9) Deficiency

Reference daily intake: 400 µg of dietary folate equivalents

Major dietary sources

- Green vegetables, legumes, fruits, beans, nuts, peas, eggs, milk, some meats, seafood, fortified grains, fortified cereals

Deficiency causes

- Alcohol use disorder, gastrointestinal disease, folate antagonists (methotrexate, trimethoprim)
- Rare for folate deficiency to be present in isolation

Neurologic manifestations

- Indistinguishable from manifestations caused by vitamin B_{12} deficiency

Laboratory tests

- Serum folate, red blood cell folate (more reliable indicator of tissue stores than serum folate), plasma homocysteine; particularly important to rule out coexisting nutrient deficiencies

Management

- 1 mg oral folate given 3 times a day initially, followed by a maintenance dose of 1 mg/d (with severe malabsorption parenteral dosing or doses up to 20 mg/d may be needed)

Additional comments

- Cooking destroys folate in food
- Depletion of the body's folate stores can occur in a few months
- Oral folate supplementation with 0.4 mg/d is recommended as prophylaxis against neural tube defects for people who may become pregnant

Methyltetrahydrofolate is required for the cobalamin-dependent remethylation of homocysteine to methionine. Methylenetetrahydrofolate is formed from tetrahydrofolate and is involved in uracil and thymine synthesis; formyltetrahydrofolate is involved in adenine and guanine synthesis. Impaired DNA synthesis caused by folate deficiency likely interferes with myelin production. Although it is found in a variety of foods, folate is easily destroyed by cooking.

DEFICIENCY CAUSES. Populations at increased risk of folate deficiency include people with alcohol use disorder, premature infants, and adolescents; increased folate requirements are seen in the setting of pregnancy, lactation, psoriasis, and chronic hemolysis. Folate deficiency may be seen in patients with small-bowel disorders associated with malabsorption; however, small intestinal bacterial overgrowth may be associated with elevated folate levels caused by bacterial synthesis. Gastric surgery, atrophic gastritis, and acid-suppressive therapy can decrease folate absorption. Methotrexate binds to dihydrofolate reductase, resulting in folate deficiency. Folate analogues such as trimethoprim and pyrimethamine can also result in folate deficiency. Numerous drugs can impair the absorption and distribution of folate. These include antimalarials, phenytoin, oral contraceptives, tetracyclines, penicillins, chloramphenicol, nitrofurantoin, and erythromycin.[20] Folate deficiency can also be seen in obesity, the cause of which is unclear.[21] Folate levels fall within weeks of decreased intake or absorption, and clinically significant depletion of folate stores is seen within months. Because it is rare to see folate deficiency in isolation, it is particularly important to screen for the deficiency of other nutrients when folate deficiency is detected.

NEUROLOGIC MANIFESTATIONS. Theoretically, folate deficiency could cause the same clinical manifestations as vitamin B_{12} deficiency. For unclear reasons, such manifestations are rare.[22] The neuropathy described with folate deficiency is typically a slowly progressive, sensory, axonal neuropathy.[23] In some studies, folate deficiency has been associated with affective disorders, particularly depression.[22] Some evidence also suggests that the elevated homocysteine accompanying folate deficiency may be associated with an increased risk of vascular complications.[22] Although these associations are poorly understood and somewhat controversial, the association of neural tube defects in babies born to folate-deficient mothers is clear.

INVESTIGATIONS AND MANAGEMENT. Serum folate levels less than 4.0 µg/L suggest a deficient state. Patients with metabolically significant folate deficiency have elevated plasma homocysteine levels. Red blood cell folate is a more reliable indicator of folate status than plasma folate because it is less affected by short-term fluctuations in folate intake, although it can be technically challenging to determine.[24]

With documented folate deficiency, a commonly used replacement regimen is 1 mg of oral folate given 3 times a day. Once the folate levels normalize, a maintenance dose of 1 mg/d orally is used. Acutely ill patients or those with severe malabsorption may need parenteral administration or doses up to 20 mg/d. Patients with drug-induced folate deficiency need folinic acid for replacement; also known as leucovorin, folinic acid is used as a “rescue” agent

KEY POINTS

- Although serum vitamin B_{12} measurement is a widely used screening test, it has technical and interpretive problems and lacks sensitivity and specificity for diagnosing vitamin B_{12} deficiency.

- Holotranscobalamin (transcobalamin-bound cobalamin) represents the metabolically active vitamin B_{12}, and its measurement can be particularly useful in equivocal cases; however, the test has limited worldwide availability.

- The presence of elevated methylmalonic acid and homocysteine levels are important indications for metabolically significant vitamin B_{12} deficiency; the former is more specific than the latter because homocysteine can also be elevated in folate deficiency.

- It is rare to see folate deficiency in isolation. It is particularly important to screen for the deficiency of other nutrients when folate deficiency is detected.

- Red blood cell folate is a more reliable indicator of folate status than plasma folate because it is less affected by short-term fluctuations in folate intake.

with folate antagonist chemotherapeutic agents such as methotrexate. Clinicians should exclude coexisting vitamin B_{12} deficiency before instituting folate therapy. Plasma homocysteine levels are used to monitor patients' response to therapy.

Thiamine

This section discusses the causes of thiamine deficiency, the neurologic manifestations of thiamine deficiency, and the management of the deficiency state (TABLE 8-3).

BACKGROUND. The terms *B_1*, *vitamin B_1*, *thiamin*, and *thiamine* are used interchangeably. The metabolically active form of thiamine is thiamine diphosphate. Thiamine diphosphate is a cofactor for the pyruvate dehydrogenase complex, alpha-ketoglutarate dehydrogenase, and transketolase. Thiamine has a role in adenosine triphosphate synthesis and energy production. The pericarp of grain and yeast is particularly rich in thiamine. Heating food can reduce its thiamine content.

DEFICIENCY CAUSES. The body's thiamine requirement is related to a person's total caloric intake and to the proportion of calories provided as carbohydrates.

TABLE 8-3

Thiamine (Vitamin B_1) Deficiency

Reference daily intake: 1.2 mg

Major dietary sources

- Whole grains, meat, fish, fortified grains, fortified cereal

Deficiency causes

- Populations or settings with increased requirements: children, pregnant or lactating patients, critical illness, hyperthyroidism, malignancy, bone marrow transplantation, systemic infection
- Marginal nutritional status: alcohol use disorder, anorexia nervosa, recurrent vomiting, starvation, extreme dieting, food fads, gastrointestinal surgery (particularly bariatric surgery), inadequate supplementation in parenteral or enteral nutrition, renal failure (particularly patients on dialysis), severe gastrointestinal disease, liver or pancreatic disease, magnesium deficiency

Neurologic manifestations

- Wernicke encephalopathy, Korsakoff psychosis, beriberi (wet or dry), Guillain-Barré syndrome–like presentation

Laboratory tests

- Red blood cell thiamine diphosphate, erythrocyte transketolase assay, serum thiamine, urine thiamine

Management

- 100 mg/d to 300 mg/d of thiamine (IV, IM, oral), significantly higher doses in some situations (Wernicke encephalopathy, alcohol use disorder, starvation)

Additional comments

- Heating food can reduce the thiamine content

IM = intramuscular; IV = intravenous.

Thiamine requirements increase during periods of high metabolic demand. Increased metabolic demand in the setting of marginal nutritional status is the typical scenario that precipitates thiamine deficiency. Often multiple contributing factors coexist. Alcohol use disorder is just one of the many causes of thiamine deficiency.[25] It has been suggested that thiamine deficiency should be considered as a possible etiology for neurologic manifestations in any critically ill patient.[26] A heavy dietary reliance on thiamine-poor carbohydrates such as polished rice or processed cassava is a risk factor for thiamine deficiency in some parts of the world. Thiamine has a short half-life, and the body can store only limited amounts; therefore, a continuous dietary supply of thiamine is necessary. A thiamine-deficient diet can result in clinically significant depletion of body stores in just 2 to 3 weeks.

NEUROLOGIC MANIFESTATIONS. The term “thiamine deficiency disorders” is used to describe the broad clinical spectrum that results from thiamine deficiency and includes neurologic, cardiovascular, gastrointestinal, and metabolic derangements.[27] The most characteristic neurologic disorders resulting from thiamine deficiency are Wernicke encephalopathy, Korsakoff syndrome or Korsakoff psychosis, and beriberi.[28,29] Wernicke encephalopathy is characterized by changes in mental status, ocular abnormalities (notably ophthalmoparesis), and ataxia, but the classic triad is rarely seen. As Wernicke encephalopathy resolves, the Korsakoff psychosis evolves. Korsakoff syndrome is characterized by an amnestic-confabulatory state. Both anterograde and retrograde amnesia may be present. These disorders are often collectively referred to as *Wernicke-Korsakoff syndrome*. They typically result from short-term and severe thiamine deficiency. The gait and trunk ataxia seen in Wernicke encephalopathy is caused by cerebellar and vestibular dysfunction, but it may be complicated by a coexisting peripheral neuropathy. Peripheral neuropathy typically results from prolonged and mild to moderate thiamine deficiency. A rapid progression that mimics Guillain-Barré syndrome is a well-described neurologic manifestation of thiamine deficiency (**CASE 8-1**).[29,30] In contrast to Guillain-Barré syndrome, thiamine deficiency–associated acute neuropathy lacks prominent autonomic manifestations or respiratory impairment. Beriberi exists in three forms: dry beriberi, wet beriberi, and infantile beriberi. Dry beriberi refers to a distal, sensorimotor, axonal neuropathy. Autonomic manifestations may be present. The term *wet beriberi* refers to when a high cardiac output heart failure causes an accompanying fluid overload. Infantile beriberi bears little resemblance to the adult form. Cardiac, aphonic, and pseudomeningitic forms are recognized.

Investigations and management

Serum or plasma thiamine and urinary thiamine levels do not accurately reflect tissue thiamine concentrations. Less than 10% of blood thiamine is contained in plasma. Measurements of erythrocyte thiamine diphosphate in the whole blood or erythrocyte transketolase activation assay are the preferred tests, but the latter has limited availability. Blood thiamine diphosphate levels of less than 70 nmol/L suggest thiamine deficiency. A normal thiamine level does not exclude thiamine deficiency as the cause of neurologic manifestations because thiamine levels normalize rapidly with oral intake. The blood draw should be done before the initiation of therapy. The presence of an anion gap metabolic acidosis and elevated lactate can be additional clues for a metabolically significant thiamine

KEY POINTS

- Health care practitioners should exclude coexisting vitamin B_{12} deficiency before instituting folate therapy in patients with folate deficiency.
- Thiamine deficiency should be considered as a possible etiology for neurologic manifestations in any critically ill patient.
- Thiamine has a short half-life, and the body can store only limited amounts; therefore, a continuous dietary supply of thiamine is necessary. A thiamine-deficient diet can result in a clinically significant depletion of the body’s stores in just 2 to 3 weeks.
- The most characteristic neurologic disorders resulting from thiamine deficiency are Wernicke encephalopathy, Korsakoff syndrome or Korsakoff psychosis, and beriberi.
- The gait and trunk ataxia seen in Wernicke encephalopathy is caused by cerebellar and vestibular dysfunction, but it may be complicated by a coexisting peripheral neuropathy.
- Peripheral neuropathy typically results from prolonged and mild to moderate thiamine deficiency. A rapid progression that mimics Guillain-Barré syndrome is a well-described neurologic manifestation of thiamine deficiency.

deficiency. MRI findings in Wernicke encephalopathy typically include an increased T2 or fluid-attenuated inversion recovery (FLAIR) signal in the paraventricular regions. Shrunken mamillary bodies may be seen in the chronic stages (Korsakoff syndrome).

Because parenteral glucose use in patients with a marginal thiamine status can consume the available thiamine and precipitate Wernicke encephalopathy,

CASE 8-1

A 35-year-old man presented with a 2-week history of ascending lower limb weakness and painful hand and foot paresthesia. The working diagnosis was Guillain-Barré syndrome. Soon after admission, he became confused. He had deficits in his mental status evaluation that included impaired recall and difficulty following complex commands. Cranial nerve examination showed bilateral impaired ocular abduction. He had mild, bilateral, proximal, and distal limb weakness. He had graduated impairment of pinprick and light touch perception to his knees and wrists. Muscle stretch reflexes were absent. Mild appendicular dysmetria and severe gait ataxia were present. A brain MRI showed a T2-signal hyperintensity in the periaqueductal gray. Nerve conduction studies and EMG showed an axonal neuropathy with acute denervation. Blood thiamine diphosphate levels were on the lower side of the normal range. It was subsequently discovered that during the preceding 2 months he had been drinking 4 to 5 glasses of wine a day, experienced a 15-pound weight loss, and his oral food intake was limited. With parenteral thiamine administration, the patient had a gradual clinical, neuroimaging, and electrophysiologic improvement.

COMMENT

Thiamine deficiency can present as a rapidly progressive ascending neuropathy that can mimic Guillain-Barré syndrome. The typical acute neurologic presentation of thiamine deficiency is changes in mental status, ophthalmoparesis, and ataxia (Wernicke encephalopathy), all of which this patient had. It is rare for the classic triad to present initially, although one or more components often develop over time. The presence of these manifestations, along with painful hand and foot paresthesia, were clues that thiamine deficiency was responsible for his rapidly progressive ascending weakness. His gait ataxia was more than what could be explained by the motor and sensory deficits and was likely because of cerebellar and possibly vestibular involvement. Thiamine deficiency (presenting as dry beriberi) should be included in the differential diagnosis of Guillain-Barré syndrome, particularly when a potential cause for thiamine deficiency is present. Blood thiamine diphosphate levels can rapidly normalize with oral intake or parenteral thiamine supplementation. Therefore, the possibility of neurologic disease caused by thiamine deficiency should not be excluded based on normal levels. Ancillary tests such as a brain MRI may show the classic neuroimaging findings seen in thiamine deficiency and provide a clue for the etiology of the weakness. The doses of parenteral thiamine are higher in the setting of alcohol use or severe malnutrition than for standard thiamine replacement.

at-risk patients should be given parenteral thiamine before administration of glucose or parenteral nutrition. Thiamine for parenteral use is diluted in 100 mL of normal saline or 5% glucose and infused over 30 minutes. A commonly used regimen for thiamine replacement is 200 mg IV every 8 hours; patients with Wernicke encephalopathy, severe malnutrition, or alcohol withdrawal should get higher doses.[32] A commonly used regimen in these patients involves giving 500 mg thiamine IV 3 times a day for 2 to 3 days, followed by 250 mg thiamine IV or IM for 3 to 5 days. Long-term oral maintenance doses range from 50 mg/d to 100 mg/d. Comorbid conditions that may have precipitated manifestations of thiamine deficiency need to be identified and treated. With wet beriberi, thiamine administration results in a prompt improvement of heart failure but a slower improvement of neuropathy. Regarding the central manifestations, ocular signs improve promptly, but gait and memory improvement are delayed. Korsakoff syndrome does not respond to thiamine administration, but spontaneous improvement may occur over time.

Niacin

This section discusses the causes of niacin deficiency, the neurologic manifestations of niacin deficiency, and the management of the deficiency state (TABLE 8-4).

Niacin (Vitamin B_3) Deficiency

TABLE 8-4

Reference daily intake: 16 mg of niacin equivalents

Major dietary sources

- Meat, poultry, fish, mushrooms, potatoes, nuts, legumes, grains, eggs, dairy products, enriched bread, fortified cereals, tryptophan-containing foods such as turkey

Deficiency causes

- Corn as a primary carbohydrate source, alcohol use disorder, carcinoid syndrome, Hartnup syndrome, vitamin B_6 deficiency, excess neutral amino acids in the diet, frequent dialysis, gut bacterial overgrowth

Neurologic manifestations

- Encephalopathy, peripheral neuropathy

Laboratory tests

- Urinary excretion of niacin metabolites (used but is not very reliable)

Management

- 25 mg to 100 mg of nicotinic acid given 3 times a day (IM, oral)

Additional comments

- Nicotinic acid has a short half-life and must be given 3 times a day
- The classic pellagra triad of dermatitis, dementia, and diarrhea is uncommon
- In nonendemic pellagra, the dermatologic and gastrointestinal manifestations are typically absent

IM = intramuscular.

BACKGROUND. The common forms of niacin are nicotinic acid and nicotinamide. Niacin is converted into nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, coenzymes that have a role in carbohydrate metabolism.[33] In humans, niacin is a product of tryptophan metabolism.

DEFICIENCY CAUSES. Niacin deficiency is common in populations that depend on corn as their primary carbohydrate because corn lacks niacin and tryptophan. Nonendemic deficiency is seen with alcohol use disorder and malabsorption. Chronic infections can increase niacin demand. In carcinoid syndrome, tryptophan is preferentially converted into serotonin, and niacin deficiency ensues. Vitamin B_6 is required for the conversion of tryptophan to niacin, and vitamin B_6 deficiency can result in niacin deficiency. Excess dietary amino acids compete with tryptophan absorption, and bacterial overgrowth converts dietary tryptophan into indoles. Hence, both of these conditions can decrease tryptophan absorption and cause subsequent niacin deficiency. Another cause of niacin deficiency is frequent dialysis. Hartnup syndrome is a metabolic disorder that affects amino acid transport and causes tryptophan deficiency, resulting in niacin deficiency.

NEUROLOGIC MANIFESTATIONS. Coexisting nutrient deficiencies make it difficult to characterize the neurologic manifestations of niacin deficiency. Encephalopathy in people with alcohol use disorder that does not respond to thiamine replacement or to treatment of suspected withdrawal with benzodiazepines should prompt consideration of niacin deficiency. The peripheral neuropathy seen in niacin deficiency is similar to that seen with thiamine deficiency. Pellagra is the classic syndromic presentation of niacin deficiency.[34] It involves the gastrointestinal tract, skin, and nervous system. The classic triad of diarrhea, dermatitis, and dementia is rarely seen; in nonendemic pellagra, the cutaneous and gastrointestinal manifestations are generally absent.

INVESTIGATIONS AND MANAGEMENT. No blood markers of niacin status are particularly reliable. Plasma nicotinamide levels from 5 ng/mL to 48 ng/mL are considered normal. Plasma metabolites of niacin, such as nicotinic acid and nicotinuric acid, can be measured. Other suggested markers include erythrocyte nicotinamide adenine dinucleotide and the urinary excretion of methylated niacin metabolites, but these are not in routine clinical use.

In deficient and symptomatic patients, 25 mg to 100 mg of nicotinic acid can be given 3 times a day orally or by IM. Known adverse effects are pruritis and a burning sensation involving the face and chest. The response of neurologic manifestations is more variable than the otherwise prompt response of dermatologic and gastrointestinal manifestations.

Pyridoxine

This section discusses the causes of pyridoxine deficiency, the neurologic manifestations of pyridoxine deficiency, and the management of the deficiency state (TABLE 8-5).

BACKGROUND. The terms *B_6*, *vitamin B_6*, and *pyridoxine* are used interchangeably. Vitamin B_6 is present as pyridoxine and pyridoxine phosphate in plant-derived foods and as pyridoxal phosphate and pyridoxamine phosphate in

KEY POINTS

- Serum or plasma thiamine and urinary thiamine levels do not accurately reflect tissue thiamine concentrations. The preferred test is to measure erythrocyte thiamine diphosphate in the whole blood.

- Because parenteral glucose use in patients with a marginal thiamine status can consume the available thiamine and precipitate Wernicke encephalopathy, at-risk patients should be given parenteral thiamine before the administration of glucose or parenteral nutrition.

- Patients with Wernicke encephalopathy, severe malnutrition, or alcohol withdrawal should get higher doses of thiamine. A commonly used regimen in these patients involves giving 500 mg thiamine IV 3 times a day for 2 to 3 days, followed by 250 mg thiamine IV or IM for 3 to 5 days.

- Encephalopathy in people with alcohol use disorder that does not respond to thiamine replacement or to the treatment of suspected withdrawal with benzodiazepines should prompt consideration for niacin deficiency. The peripheral neuropathy seen in niacin deficiency is similar to that seen with thiamine deficiency.

animal-derived foods. Pyridoxal and pyridoxal phosphate are the main circulating forms of vitamin B_6. Pyridoxine functions as a prosthetic group for many cellular enzymatic reactions. It serves as a cofactor for enzymes involved in metabolizing amino acids, lipids, nucleic acid, and one-carbon units.[35] It is also involved in gluconeogenesis, glycolysis, neurotransmitter synthesis, and heme biosynthesis. Food processing reduces the bioavailability of vitamin B_6.

DEFICIENCY CAUSES. Pyridoxine deficiency is seen with malnutrition, malabsorption, alcohol use disorder, and chronic illness. Individuals at risk of developing vitamin B_6 deficiency include older adults and pregnant and lactating patients. Antiseizure medications such as carbamazepine and phenytoin increase the catabolism of pyridoxine. Vitamin B_6 deficiency is also associated with use of hydrocortisone, cyclosporin, cycloserine, isoniazid, hydralazine, and penicillamine.

NEUROLOGIC MANIFESTATIONS. In infants, pyridoxine deficiency can cause seizures; pyridoxine-dependent epilepsy results from certain genetic disorders of pyridoxine metabolism. Adults are more tolerant of vitamin B_6 deficiency than infants. Even with low levels, symptoms caused by vitamin B_6 deficiency are rare. Peripheral neuropathy may be seen. Vitamin B_6 deficiency can also cause microcytic hypochromic anemia. Excess vitamin B_6 consumption, often in doses of 100 mg/d to 200 mg/d for prolonged periods, has been reported to cause a sensory ganglionopathy characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensation, and a positive Romberg sign.[36] Pyridoxine toxicity may also cause nausea, vomiting, diarrhea, and rash.

Pyridoxine (Vitamin B_6) Deficiency

TABLE 8-5

Reference daily intake: 1.7 mg

Major dietary sources

- Meat, fish, poultry, legumes, tofu, fruits (excluding citrus), eggs, nuts, dairy products, starchy vegetables, whole grains

Deficiency causes

- Alcohol use disorder, malabsorption, vitamin B_6 antagonists

Neurologic manifestations

- Peripheral neuropathy, seizures (in infants)

Laboratory tests

- Plasma pyridoxal phosphate

Management

- 50 mg/d to 100 mg/d of pyridoxine (oral)

Additional comments

- Vitamin B_6 toxicity is characterized by sensory neuronopathy
- Vitamin B_6 supplementation is given to patients on medications such as isoniazid to prevent neuropathy
- Food processing reduces the bioavailability of vitamin B_6

INVESTIGATIONS AND MANAGEMENT. Vitamin B_6 status is assessed by measuring its levels in plasma or urine. The most commonly used measures are plasma pyridoxal phosphate and plasma pyridoxic acid, with normal values being 5 μg/L to 50 μg/L and 3 μg/L to 30 μg/L, respectively. Functional indicators of vitamin B_6 status that are based on pyridoxal phosphate-dependent reactions and tests for assessing long-term pyridoxine status exist, but these are not commonly used in clinical practice.

Vitamin B_6 is supplemented in a dose of 50 mg/d to 100 mg/d orally to prevent the development of neuropathy in individuals on drugs that may cause vitamin B_6 deficiency. The neuronopathy associated with vitamin B_6 toxicity can gradually improve with the timely cessation of vitamin B_6.

Vitamin E

This section discusses the causes of vitamin E deficiency, the neurologic manifestations of vitamin E deficiency, and the management of the deficiency state (TABLE 8-6).

BACKGROUND. α-Tocopherol is the active form of vitamin E. Vitamin E is a lipid-soluble antioxidant and free radical scavenger. It is essential for physiologic processes such as the permeability of lipid bilayers, cell adhesion, and gene expression.[37] Leafy vegetables and vegetable oils are important dietary sources.

DEFICIENCY CAUSES. Vitamin E deficiency is seen with pancreatic insufficiency, chronic cholestasis, and other causes of malabsorption. Many years of acquired

TABLE 8-6

Vitamin E Deficiency

Reference daily intake: 15 mg

Major dietary sources

- Vegetable oils, green leafy vegetables, whole grains, nuts

Deficiency causes

- Malabsorption caused by liver or pancreatic disease

Neurologic manifestations

- Myeloneuropathy, peripheral neuropathy
- Resembles Friedreich ataxia

Laboratory tests

- Serum vitamin E
- Correction needed in the presence of hyperlipidemia

Management

- Broad dose range depending on etiology and severity
- Bile salt supplementation may be of additional benefit

Additional comments

- By the time neurologic manifestations caused by vitamin E deficiency appear, the serum levels are severely reduced

fat malabsorption are required to deplete vitamin E stores. Vitamin E supplementation in total parenteral nutrition may be inadequate to maintain stores. Only rarely is vitamin E deficiency caused by true dietary insufficiency. Childhood-onset diseases such as ataxia with vitamin E deficiency, abetalipoproteinemia, hypobetalipoproteinemia, and chylomicron disease can have neurologic manifestations caused by vitamin E deficiency, often in conjunction with growth retardation and ocular manifestations.

NEUROLOGIC MANIFESTATIONS. The prototypic neurologic manifestation of vitamin E deficiency is a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement.[37] Ptosis, pigmentary retinopathy, and ophthalmoparesis may be seen. The phenotype is similar to that of Friedreich ataxia. The neuropathy seen in vitamin E deficiency is generally associated with central nervous system involvement. A demyelinating neuropathy with spinocerebellar manifestations has been reported.[38] Swollen dystrophic axons (spheroids) may be seen in the gracile and cuneate nuclei; lipofuscin may accumulate in the sensory neurons of the dorsal root ganglia and peripheral Schwann cell cytoplasm. A myopathy characterized by inflammatory infiltrates and rimmed vacuoles has also been described.[39]

INVESTIGATIONS AND MANAGEMENT. In adults, serum vitamin E levels of 5.5 mg/L to 17 mg/L represent the normal range. Values less than 3.0 mg/L indicate significant deficiency. In patients with neurologic manifestations caused by vitamin E deficiency, the vitamin E levels are severely reduced. Hyperlipidemia increases plasma carriers for vitamin E and can therefore increase vitamin E levels without it being a true reflection of vitamin E stores.[37] Cholestatic liver disease can result in hyperlipidemia, and normal vitamin E levels in this situation may be false-negative. In such situations, effective serum vitamin E concentration can be calculated by dividing the serum vitamin E by the total of serum cholesterol and triglycerides.[40] MRI in vitamin E deficiency-related neuropathy or myeloneuropathy may show dorsal column T2 signal hyperintensity.

In the presence of fat malabsorption, IM administration of a water-miscible product of vitamin E in doses as high as 10 mg/kg to 100 mg/kg of α-tocopherol may be required. In other situations, oral replacement in a dose of 300 mg/d may suffice. Some patients may additionally benefit from bile salt supplementation.

Copper

This section discusses the causes of copper deficiency, the neurologic manifestations of copper deficiency, and the management of the deficiency state (TABLE 8-7).

BACKGROUND. Copper is a component of enzymes that play a key role in maintaining the structure and function of the nervous system. These include cytochrome c oxidase, copper-zinc superoxide dismutase, tyrosinase, dopamine β-hydroxylase, lysyl oxidase, peptidylglycine α-amidating monooxygenase, and monoamine oxidase.

DEFICIENCY CAUSES. The low daily requirement and ubiquitous distribution of copper in food make clinically significant acquired copper deficiency rare. The most common cause of acquired copper deficiency is a prior history of gastric

KEY POINTS

- Symptoms caused by vitamin B_6 deficiency are rare even in the setting of low levels. Peripheral neuropathy may be seen, and vitamin B_6 deficiency can also cause microcytic hypochromic anemia.
- Excess vitamin B_6 consumption, often in doses of 100 mg/d to 200 mg/d for prolonged periods, has been reported to cause a sensory ganglionopathy characterized by sensory ataxia, areflexia, multimodal sensory impairment, and a positive Romberg sign.
- Many years of acquired fat malabsorption are required to deplete vitamin E stores. Only rarely is vitamin E deficiency caused by true dietary insufficiency.
- The prototypic neurologic manifestation of vitamin E deficiency is a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement. Ptosis, pigmentary retinopathy, and ophthalmoparesis may be seen. The phenotype is similar to that of Friedreich ataxia.
- The most common cause of acquired copper deficiency is a prior history of gastric surgery for peptic ulcer disease or bariatric surgery.
- Copper deficiency may be seen with celiac disease even in the absence of gastrointestinal manifestations.

surgery for peptic ulcer disease or bariatric surgery.[41-45] Current guidelines emphasize the importance of monitoring copper status in high-risk individuals following bariatric surgery.[46,47] Copper deficiency can result from other causes of malabsorption, particularly gastrointestinal diseases. Copper deficiency is seen with celiac disease even in the absence of gastrointestinal manifestations. Excess zinc ingestion is a well-recognized cause of copper deficiency.[48] Zinc decreases copper absorption and is used to manage Wilson disease, a hereditary disorder characterized by copper overload. Zinc has been empirically used for common cold prevention and for various other ailments with minimal evidence of efficacy. Unusual sources of excess zinc have included zinc-containing denture adhesives and swallowing of zinc-containing coins.[49,50] Overloading with parenteral zinc during hemodialysis can result in copper deficiency. Overtreatment of the copper toxicity of Wilson disease with zinc can cause copper deficiency with attendant neurologic manifestations.[51]

NEUROLOGIC MANIFESTATIONS. The neurologic manifestations of copper deficiency are typically delayed by years after the inciting event. Unlike thiamine and folate, and like vitamin B_{12}, body copper stores deplete over years. The most common neurologic manifestation of acquired copper deficiency is myelopathy or myeloneuropathy, which resembles the subacute combined degeneration seen with vitamin B_{12} deficiency (CASE 8-2).[51,52] Also reported is progressive,

TABLE 8-7 **Copper Deficiency**

Reference daily intake: 0.9 mg

Major dietary sources

- Shellfish, nuts, seeds, whole-grain products, beans, mushrooms, cocoa, chocolate

Deficiency causes

- Gastric surgery (particularly bariatric surgery or surgery for peptic ulcer disease), zinc toxicity, gastrointestinal disease, total parenteral and enteral nutrition

Neurologic manifestations

- Myelopathy, myeloneuropathy, optic neuropathy

Laboratory tests

- Serum copper, urinary 24-hour copper excretion, serum ceruloplasmin, serum zinc, urinary 24-hour zinc excretion, hematologic parameters (anemia, neutropenia, vacuolated myeloid precursors, ringed sideroblasts, iron-containing plasma cells)

Management

- Oral elemental copper: 8 mg/d for the first week, 6 mg/d for the second week, 4 mg/d for the third week, and 2 mg/d thereafter
- Parenteral copper: 2 mg/d elemental copper IV for 5 days and periodically thereafter

Additional comments

- Oral iron can interfere with copper absorption
- Celiac disease can cause copper deficiency in the absence of gastrointestinal manifestations

IV = intravenous.

asymmetric weakness or electrodiagnostic evidence suggestive of lower motor neuron disease.[49,54] Optic nerve involvement has been rarely reported. Although typically myelopathy or myeloneuropathy is seen, a predominantly axonal, length-dependent sensory-predominant peripheral neuropathy has also been reported.[55] Hematologic manifestations can include anemia, neutropenia, and thrombocytopenia. Pancytopenia may occur, and patients may be diagnosed as having a myelodysplastic syndrome.

CASE 8-2

A 44-year-old woman was evaluated for a 3-year history of imbalance and distal lower limb paresthesia. She had gastric bypass surgery a decade prior, and she had been on vitamin B_{12} supplementation since then. Her neurologic examination was suggestive of a myeloneuropathy with dorsal column, corticospinal tract, and peripheral nerve involvement. The key findings included impaired perception of position at her toes, impaired vibration perception to her knees, brisk knee jerk, decreased ankle jerk, an extensor plantar response, and a spastic ataxic gait. Electrophysiologic studies included EMG, nerve conduction studies, and somatosensory evoked potentials; these showed evidence of a mild axonal peripheral neuropathy and central conduction delay that localized to the cervical spinal cord. No abnormalities were noted on the spinal cord MRI. Blood work revealed a mild normocytic anemia and neutropenia with normal vitamin B_{12} and methylmalonic acid levels, but a low copper level of 4 μmol/L.

COMMENT

Vitamin B_{12} deficiency is common after bariatric surgery, and patients routinely receive vitamin B_{12} supplementation after surgery. Without vitamin B_{12} replacement, it takes about 3 to 5 years for the body's vitamin B_{12} stores to be depleted. Copper deficiency can cause a myeloneuropathy that is identical to the myeloneuropathy caused by vitamin B_{12} deficiency. Both vitamin B_{12} and copper deficiency can coexist. Hence, it is important to check for copper deficiency in patients who present with a myeloneuropathy after bariatric surgery, particularly when no laboratory evidence of vitamin B_{12} deficiency is present or when patients with vitamin B_{12} deficiency continue to deteriorate despite vitamin B_{12} replacement. Either condition can be associated with hematologic manifestations. Neurologic manifestations in the absence of hematologic derangement are well recognized with both copper and vitamin B_{12} deficiency. The prolonged use of zinc in high doses can also cause copper deficiency. The presence of both malabsorption and zinc ingestion can increase the likelihood of clinically significant copper deficiency. Increased T2 signal in the dorsal columns, and in some cases also the corticospinal tracts, can be seen with either condition, but neurologic manifestations can occur without MRI abnormalities. Generally, high-dose oral copper supplementation is adequate; in some cases, parenteral therapy is required. Response to the hematologic manifestations is prompt and complete, and the response of neurologic manifestations is variable, but typically this treatment approach prevents continued neurologic deterioration.

INVESTIGATIONS AND MANAGEMENT. Laboratory markers for copper deficiency include a decrease in both serum copper and urine 24-hour copper excretion. The normal range for serum copper in adults is 75 μg/dL to 145 μg/dL. Serum ceruloplasmin generally parallels serum copper levels. It is important to remember that Wilson disease presents with decreased serum copper and ceruloplasmin, and serum copper and ceruloplasmin may be reduced in carriers of the Wilson disease gene.[56] However, these patients have elevated urine 24-hour copper excretion. In Wilson disease, tissue copper stores are increased, and determining the liver copper level can be especially useful in equivocal cases. Also, ceruloplasmin is an acute-phase reactant and can be increased in settings such as pregnancy, oral contraceptive use, liver disease, malignancy, uremia, myocardial infarction, hematologic disease, and various infectious and inflammatory states. A corresponding increase in serum copper often occurs, but this does not imply copper toxicity because the copper is predominantly bound copper. Toxicity in Wilson disease results from free copper, which is not a routinely performed laboratory determination. Additional tests such as blood cell count, serum and urine 24-hour zinc excretion, and testing for other nutrient deficiencies (particularly vitamin B_{12}) can aid the overall management of patients with copper deficiency. The neuroimaging features in copper deficiency myeloneuropathy are identical to those that present with vitamin B_{12} deficiency and include T2 signal hyperintensity in the dorsal columns and, less commonly, the lateral corticospinal tracts.[57]

Oral copper supplementation in doses ranging from 2 mg/d to 8 mg/d is commonly used. Indications for parenteral therapy include severe malabsorption, as can be seen in short bowel syndrome, rapid neurologic deterioration, significant hematologic derangement, severe and prolonged copper depletion, and failure of oral therapy. The most commonly used parenteral therapy regimen involves giving 2 mg of elemental copper IV daily for 5 days, and periodically thereafter. Some have used initial parenteral therapy followed by oral therapy. Although addressing other nutrient deficiencies remains important, oral iron therapy can cause impaired copper absorption. Response of the hematologic parameters is prompt and often complete; recovery of the neurologic derangements is more variable and often delayed.

SPECIAL POPULATIONS

This section discusses nutritional deficiency in special settings, particularly bariatric surgery, alcohol use disorder, and malabsorption.

Obesity, Metabolic Syndrome, and Bariatric Surgery

The rates of bariatric surgery and its subsequent neurologic complications have grown with the obesity epidemic.[58] Obesity, somewhat paradoxically, can be associated with nutrient deficiencies.[59] Even without identified nutritional deficiencies, both obesity and diabetes are recognized metabolic drivers of peripheral neuropathy.[60] In a Mayo Clinic study of 435 patients who had bariatric surgery, 16% developed peripheral neuropathy.[61] The neuropathy patterns identified included a sensory-predominant peripheral neuropathy, mononeuropathy, and radiculoplexus neuropathy. Although malnutrition is the most important risk factor, neuropathy soon after bariatric surgery can be caused by perioperative inflammatory neuropathies or stretch- and compression-related injuries. Weight loss from bariatric surgery may make the peroneal nerve more

vulnerable to compression at the fibular head, resulting in footdrop. Thiamine deficiency causes early neurologic problems after bariatric surgery, whereas delayed neurologic problems result from vitamin B_{12} deficiency (in those not on vitamin B_{12} replacement) or copper deficiency.[62] A recent meta-analysis of 11 studies examining 1494 patients who had undergone bariatric surgery noted thiamine deficiency in 27% of patients.[63] Nutritional complications following bariatric surgery are more common after procedures such as Roux-en-Y gastric bypass as compared with predominantly restrictive procedures such as sleeve gastrectomy or adjustable gastric band placement.

Alcohol Use Disorder

Alcohol is known to affect the central and peripheral nervous systems in various ways. Peripheral neuropathy in the context of alcohol use disorder can be caused by nutritional deficiencies (often multiple) or alcohol-related neurotoxicity. Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential small-fiber dysfunction.[64,65] Before attributing a peripheral neuropathy to alcohol use disorder, clinicians should rule out coexisting nutrient deficiency. Thiamine-deficiency–related neuropathy is often a more rapidly progressive process with large-fiber sensory dysfunction. The pathophysiology of alcoholic myopathy is poorly understood.[66] Whether alcohol can directly cause dementia is controversial. Wernicke encephalopathy and its sequelae of Korsakoff psychosis and alcohol-related cerebellar degeneration are the most characteristic neurologic complications of alcohol use disorder. Acute neurologic presentations related to alcohol are caused by intoxication or withdrawal. Marchiafava-Bignami disease is a poorly understood neurologic complication of alcohol use disorder characterized by the preferential involvement of the corpus callosum. Clinical features of this disorder include changes in mental status, memory impairment, imbalance, and features of interhemispheric disconnection that reflect the predilection for the corpus callosum.

Malabsorption

Nutritional deficiencies are commonly seen in inflammatory bowel disease (ulcerative colitis or Crohn disease), celiac disease, and other gastrointestinal disorders associated with malabsorption, including gastrointestinal surgeries. Neurologic manifestations associated with inflammatory bowel disease may be related to the primary disease, coincidental, or a consequence of disease complications or treatment. Terminal ileum involvement is common in Crohn disease and may require resection. Vitamin B_{12} absorption occurs in the distal ileum, making this subgroup vulnerable to manifestations of vitamin B_{12} deficiency. Peripheral neuropathy is the most common neurologic complication of inflammatory bowel disease and may be immune-mediated, related to nutrient deficiency, or caused by antitumor necrosis factor-alpha or metronidazole therapy.[5,67-69]

Celiac disease is an immune-mediated enteropathy triggered by ingesting gluten-containing grains in genetically susceptible individuals.[70] The major predisposing genes are *HLA-DQ2* and *HLA-DQ8*. It is characterized by mucosal inflammation and resulting malabsorption. The overall prevalence of celiac disease in the general population is believed to be about 1%; subclinical disease is likely more common. Neurologic complications occur in approximately 10% of

KEY POINTS

- **Excess zinc ingestion is a well-recognized cause of copper deficiency. Zinc decreases copper absorption and is used to manage Wilson disease, a hereditary disorder characterized by copper overload.**
- **The most common neurologic manifestation of acquired copper deficiency is myelopathy or myeloneuropathy, which resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.**
- **Thiamine deficiency causes early neurologic problems after bariatric surgery, whereas delayed neurologic problems result from vitamin B_{12} deficiency (in those not on vitamin B_{12} replacement) or copper deficiency.**
- **Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential small-fiber dysfunction.**

patients with celiac disease[71]; these may be caused by a specific nutrient deficiency or immunologic mechanisms. Severe malabsorption is uncommon in patients with a neurologic presentation. Neurologic manifestations may be unaccompanied by gastrointestinal symptoms. In the absence of gastrointestinal symptoms or small-bowel biopsy abnormalities, gluten sensitivity rather than celiac disease is implicated in neurologic manifestations. In some of these cases, neurologic manifestations may be followed by intestinal manifestations. Ataxia and peripheral neuropathies are the most characteristic neurologic manifestations of celiac disease.[5,71,72]

Once IgA deficiency is excluded, the presence of IgA class antitransglutaminase 2 antibodies is extremely sensitive and specific for celiac disease.[73] The specificity of IgA antiendomysial antibody is even higher than IgA antitransglutaminase 2, but variable results are related to technical factors. IgG class antideamidated gliadin peptide is less sensitive and specific but may have a role in selective IgA deficiency. The utility of antigliadin antibodies for celiac disease is limited because between 10% to 20% of the general population may have these antibodies. Serologic tests may resolve, and histologic findings may improve with the removal of dietary gluten. Generally, the response of neurologic manifestations is less robust to a gluten-free diet than the gastrointestinal manifestations. In some patients with neurologic manifestations, immunosuppressive therapy has been tried empirically with generally negative results.[74] Coexisting vitamin or mineral deficiencies in association with celiac disease should be looked for and treated appropriately.

CONCLUSION

Nutritional neuropathies are a treatable group of disorders requiring prompt diagnosis and therapy to optimize outcomes. Multiple nutrient deficiencies often coexist. Identification of a nutrient deficiency requires an aggressive search for the underlying etiology. At times more than one cause for the deficiency state may be present. Often, other parts of the nervous system may be involved, and systemic manifestations, if present, may provide an indication as to the underlying etiology of the peripheral neuropathy. Long-term therapy and close follow-up are essential to prevent relapse.

Obesity can be associated with nutrient deficiencies. The rising use of bariatric surgery makes it particularly important to be familiar with recognizing and managing nutritional neuropathies. A high index of suspicion is necessary for this group of patients and other at-risk populations such as those with gastrointestinal disease, older adults, people with food insecurity, and those with malnutrition in the setting of alcohol use disorder.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Paraproteinemic Neuropathies

By Said R. Beydoun, MD, FAAN; Leila Darki, MD

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Address correspondence to Dr Said R. Beydoun, USC Healthcare Consultation Center II, 1520 San Pablo St, Ste 3000, Los Angeles, CA 90033, sbeydoun@usc.edu.

RELATIONSHIP DISCLOSURE:
Dr Beydoun has received personal compensation in the range of $500 to $4999 for serving as a consultant for Amylyx Pharmaceuticals, Biogen, Mitsubishi Chemical Group Corporation, Octapharma USA, Inc, and UCB S.A. and on a speakers bureau for Grifols S.A.; in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, Alnylam Pharmaceuticals, Inc, argenx, Janssen Global Services, LLC, and Takeda Pharmaceutical Company Ltd and on speakers bureaus for Amylyx Pharmaceuticals and CSL; and in the range of $10,000 to $49,999 for serving as a consultant for CSL and on speakers bureaus for Alexion Pharmaceuticals, Inc, Alnylam Pharmaceuticals, Inc, argenx, and Takeda
Continued on page 1513

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Beydoun and Darki discuss the unlabeled/investigational use of ibrutinib, IV immunoglobulin, and rituximab for the treatment of IgM-myelin-associated glycoprotein polyneuropathy.

ABSTRACT

OBJECTIVE: Coexistence of polyneuropathy and gammopathy is a common but potentially challenging situation in clinical practice. This article reviews the clinical, electrophysiologic, and hematologic phenotypes of the paraproteinemic neuropathies and the diagnostic and treatment strategies for each.

LATEST DEVELOPMENTS: Advances in our understanding of the underlying pathophysiology of various paraproteinemic neuropathies and their corresponding phenotypes have identified potential new therapeutic targets. Therapeutic strategies to diminish anti–myelin-associated glycoprotein (MAG) IgM antibodies have shown partial and inconsistent efficacy; however, antigen-specific immune therapy is being investigated as a novel treatment to remove the presumably pathogenic anti-MAG antibody. Advances in genetic and cell signaling studies have resulted in the approval of Bruton tyrosine kinase inhibitors for Waldenström macroglobulinemia. Monoclonal antibodies are being investigated for the treatment of light chain amyloidosis.

ESSENTIAL POINTS: Early recognition and treatment of underlying plasma cell disorders improves clinical outcomes in patients with paraproteinemic neuropathy. Despite significant progress, our knowledge regarding underlying mechanisms for paraproteinemic neuropathy is still limited. Clinicians' awareness of clinical phenotypes, electrophysiologic hallmarks, and hematologic findings of the different paraproteinemic neuropathies is crucial to promptly identify and treat patients and to avert misdiagnosis. Multidisciplinary collaboration among specialists, including neurologists and hematologists, is paramount for the optimal treatment of these patients with overlapping conditions.

INTRODUCTION

Paraproteinemic peripheral polyneuropathies are a heterogeneous group of neuropathies that share the common thread of a homogeneous immunoglobulin in the serum. They have distinct neurologic and hematologic findings, a wide spectrum of clinical presentations, and diverse natural histories. TABLE 9-1 summarizes the characteristic features of common paraproteinemic peripheral polyneuropathies.

Because both polyneuropathy and monoclonal gammopathy are common, concurrence does not always imply causation, and the incidental presence of a paraprotein can sometimes be misleading and result in erroneous therapy.

Common Paraproteinemic Neuropathy Clinical Manifestations, Electrodiagnostic Findings, Serologic Markers, and Treatment

TABLE 9-1

Diseases	Paraprotein type	Predominant neuropathic manifestation	Electrophysiologic features	Serum antibodies or other supportive diagnostic tests	Treatment
IgM anti–myelin-associated glycoprotein (MAG), paraproteinemic peripheral neuropathy	IgM, usually kappa	Distal sensory, sensory ataxia, mild distal weakness	Prolonged distal motor latency, low terminal latency index	Anti-MAG (50-65%)	Mild: Supportive Progressive: Rituximab, IV immunoglobulin (IVIg)
Waldenström macroglobulinemia peripheral neuropathy	IgM	Sensory ataxia, sensorimotor (distal predominance)	Prolonged distal motor latency, low terminal latency index, axonal or mixed axonal and demyelinating	Anti-MAG (50%)	Rituximab, alkylating agents, proteasome inhibitors, dexamethasone, ibrutinib, stem cell transplantation, plasma exchange (for hyperviscosity syndrome and severe cryoglobulinemia)
CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies)	IgM	Sensory ataxia and motor weakness involving ocular motor and bulbar muscles	Demyelinating > axonal	Disialosyl antibodies	IVIg, rituximab
POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome	IgA > IgG, lambda	Painful sensory symptoms in the feet with distal muscle weakness and atrophy	Demyelinating, conduction block not common	Vascular endothelial growth factor > 200 pg/mL, thrombocytosis	Radiation, hematopoietic cell transplantation, daratumumab, bortezomib, lenalidomide
Light chain amyloidosis peripheral neuropathy	Lambda	Length-dependent, sensory-predominant (early predilection for small-diameter sensory and autonomic fibers)	Mainly axonal	Biopsy of affected tissue with amyloid subtyping	Address underlying plasma cell dyscrasia: high-dose chemotherapy, stem cell transplantation Emerging: Removing amyloid deposits and inhibiting amyloid fibril formation, immune therapies
Type I cryoglobulinemia peripheral neuropathy	IgM > IgG > IgA > light chain	Painful sensory neuropathy	Predominantly small fibers sparing autonomic nerves	Cryoglobulins	Address underlying hematologic condition

IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M.

However, the presence of paraprotein should not be overlooked because it may have a significant impact on the diagnosis, management, and prognosis of the neuropathy.[1]

This practical review aims to delineate the various clinical phenotypes of paraproteinemic peripheral polyneuropathies, as well as specific diagnostic and therapeutic considerations.

PARAPROTEINEMIA

The monoclonal gammopathy or paraproteinemia is produced by an abnormal clonal proliferation of plasma cells or B cells, which may or may not occur in the context of hematologic malignancy. These monoclonal proteins exist as heavy chain subtypes (IgG, IgA, IgM, and, less commonly, IgD or IgE) and light chain subtypes (kappa or lambda).[1] The monoclonal protein is detectable by serum or urine protein electrophoresis, where the abnormal paraprotein appears as a band or spike.[2] When light chains alone are produced by plasma cells, they may be detected in the serum or urine (when noted in the urine, they are called *Bence-Jones proteins*).[3]

A wide range of mature B cell disorders may be associated with a circulating paraprotein. Paraproteins most commonly occur as a monoclonal gammopathy of undetermined significance (MGUS).[3] MGUS is characterized by the presence of a monoclonal paraprotein in the blood (less than 3 g/dL), plasma cells less than 10% on bone marrow examination, and a lack of characteristic end-organ damage that is seen in multiple myeloma (hyper**c**alcemia, **r**enal failure, **a**nemia, or **b**one lesions [CRAB]) or Waldenström macroglobulinemia.[2] The prevalence of MGUS increases with age, affecting 3.2% of people older than 50 years, increasing to 8.9% in people older than 85 years.[2]

A monoclonal gammopathy becomes clinically significant when end-organ damage develops. Commonly associated hematologic disorders are summarized in (TABLE 9-2).

The risk of progression of MGUS to myeloma or another related disorder is 1% per year.[3] The monoclonal protein level should be determined every 4 to 6 months for approximately 1 to 2 years after identification of the monoclonal

TABLE 9-2 **Hematologic Disorders Associated With Paraproteins**

Multiple myeloma
POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome
Plasmacytoma (solitary, extramedullary, or multiple)
Lymphoproliferative disorders
◆ Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)
◆ Chronic lymphocytic leukemia
Primary light chain amyloidosis
Heavy chain disease
Light chain disease

gammopathy followed by further periodic testing every 6 to 12 months depending on the risk factors.[4]

Paraproteinemic Neuropathies

Approximately 10% of patients with otherwise idiopathic neuropathy have paraproteinemia.[5]

Because paraproteins and neuropathy are common and frequently coexist, it is very important to distinguish an incidental occurrence from a causative association. Paraproteinemic neuropathies more commonly occur with IgM (50% to 75%) than with IgG or IgA monoclonal protein[6]; thus, the likelihood of a causal role of a paraprotein is increased if the paraprotein is of IgM subtype.[6,7] The presence of systemic symptoms, rapidly progressive neuropathy, autonomic dysfunction, laboratory abnormalities (anemia, thrombocytopenia, thrombocytosis), and demyelinating neuropathies are important helpful clues to look for.

Several pathophysiologic mechanisms are implicated in paraproteinemic peripheral polyneuropathies, as listed in **TABLE 9-3**.[6,8,9]

Diagnostic Evaluation

Searching for paraproteinemia should be part of a routine diagnostic evaluation of a patient with a diagnosis of polyneuropathy.[10] Serum immunofixation electrophoresis is a much more sensitive method for the detection of paraproteinemia than serum protein electrophoresis and should be routinely performed whenever a diagnosis of paraproteinemia is considered.[11] Urine immunofixation studies and evaluation for the presence of Bence-Jones proteins increase sensitivity.[10] Serum free light chain measurement and ratio should be determined.[10] If the free light chain value is abnormal, even without monoclonal gammopathy, urine studies are important, specifically in the setting of the suspicion of light chain (AL) amyloidosis. The amount of the monoclonal protein

Mechanisms of Nerve Damage in Paraproteinemia TABLE 9-3

Mechanism	Disorders
Interaction of antibodies with specific antigenic targets on peripheral nerves	IgM anti-myelin-associated glycoprotein neuropathy, CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies)
Monoclonal protein deposition	Light chain amyloidosis
Overproduction of inflammatory cytokines	POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome
Infiltration of peripheral nerve by malignant cells	Neurolymphomatosis
Ischemic	Cryoglobulinemic vasculitis
Compressive	Plasma cell expansion in multiple myeloma, infiltration of ligamentous tissue (amyloid light chain) directly compressing adjacent nerves
Treatment related	Thalidomide- and bortezomib-induced neuropathy

IgM = immunoglobulin M.

should be quantified in both serum and urine if a monoclonal protein is identified.[4]

Once a paraprotein is identified, the next step is to determine if the neuropathy is related to gammopathy and to identify the underlying hematologic condition. A low threshold for referral to a hematologist should be considered for all patients with a paraproteinemia.[12]

A thorough physical examination, evaluating for lymphadenopathy, hepatosplenomegaly, macroglossia, and other signs of systemic disorders, such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome or amyloidosis, is necessary.[10]

Obtaining a complete blood cell count, renal and liver function tests, calcium and phosphorus levels, erythrocyte sedimentation rate, and urinalysis to assess for end-organ damage is required. Other recommended tests include C-reactive protein, rheumatoid factor, β_2-microglobulin, and uric acid level.[13]

A skeletal survey to evaluate for lytic or sclerotic lesions is recommended, particularly for non-IgM monoclonal gammopathy.[13] This is usually performed with conventional x-rays or low-dose CT.[10]

Bone marrow is usually examined for all patients with a monoclonal protein level of more than 15 g/L, although some hematologists perform it on most patients with monoclonal gammopathies.[4]

Detailed electrophysiologic testing defines the pathophysiology of the neuropathy, with close attention to certain parameters such as distal motor latencies, motor nerve conduction velocities, terminal latency index (distal nerve conduction distance/[proximal motor conduction velocity × distal motor latency]), assessment for the presence of conduction block, and abnormal compound muscle action potential (CMAP) temporal dispersion.[12,13]

CSF analysis including cytology and neuroimaging studies (MRI with and without contrast of affected nerve roots, positron emission tomography [PET]-CT scan of the affected plexus, and ultrasonography of the proximal nerves) are recommended, specifically when leptomeningeal infiltration is suspected.[6,14]

Nerve and muscle biopsies are occasionally considered if neurolymphomatosis, vasculitis, or AL amyloidosis is suspected and not identified in other tissue biopsies.[6,12]

Skin biopsy to determine intraepidermal nerve fiber density may be helpful to assess small fiber nerve loss.[12] In the clinical context of prominent small fiber and autonomic neuropathy symptoms, abnormal intraepidermal nerve fiber density or autonomic function testing in a patient with a monoclonal gammopathy should raise the suspicion of possible AL amyloidosis and trigger further investigation.[15] Abdominal fat aspirates and other tissue biopsies to evaluate for the presence of amyloid are important in the diagnostic evaluation of AL neuropathy.

ANTI–MYELIN-ASSOCIATED GLYCOPROTEIN PERIPHERAL NEUROPATHY

Anti–myelin-associated glycoprotein (MAG) neuropathy usually manifests as a male-predominant, late-onset, slowly progressive, distal polyneuropathy primarily affecting large sensory fibers.[14] It is most associated with IgM monoclonal gammopathy. Cardinal manifestations include early sensory ataxia, resulting in gait impairment with absent or mild distal weakness and frequent association with tremor.[12,16] The phenotype is known as *distal acquired*

demyelinating symmetric neuropathy (DADS) with monoclonal protein.[17] DADS with monoclonal protein resembles the distal CIDP (chronic inflammatory demyelinating polyradiculoneuropathy) variant, known as *idiopathic DADS*. However, when associated with IgM MAG antibodies, it is considered a different disease from CIDP.

Fifty percent to 65% of patients with DADS with monoclonal protein have high titers of anti-MAG antibody, which is most commonly a kappa light chain. Some patients may have antibodies directed against gangliosides or ganglioside complex.[18] About 35% of patients with IgM neuropathy do not have any identifiable antibody and are classified as having non–anti-MAG DADS with monoclonal protein.[6,17] However, these patients may have a clinical and electrodiagnostic phenotype similar to anti-MAG polyneuropathy.[17]

MAG is a 100-kDa transmembrane protein, a glycoprotein of the central and peripheral nerve myelin localized in periaxonal Schwann cell and oligodendroglial membranes of myelin sheaths; it plays an important role in the formation of myelin and the interaction between axons and myelin.[19] The capacity of the anti-MAG antibodies to cause demyelination has been documented in multiple studies, providing evidence that these antibodies are causally related to the neuropathy.[18-21] However, targeted therapy with further reduction in anti-MAG antibodies fails to show sustained clinical improvement, requiring further research to identify the exact underlying pathologic mechanisms.

DADS with monoclonal protein usually has a benign course with mild functional deterioration over time; however, the prognosis is variable,[12] with reported disability (increasing tremor and ataxia) rates of 16% at 5 years, 24% at 10 years, and 50% at 15 years.[22]

The cutoff diagnostic value recommended by a commercial enzyme-linked immunosorbent assay (ELISA) manufacturer used to detect anti-MAG antibody is 1000 Bühlmann titer units (BTU); however, studies to assess the ELISA sensitivity and specificity at different thresholds demonstrated a better combination of sensitivity and specificity at a threshold more than 1500 BTU with the best value of specificity obtained at threshold more than 7000 BTU.[23]

Nerve conduction studies demonstrate a uniformly slow conduction velocity with characteristic prolonged distal latencies and short terminal latency index, indicating accentuated distal conduction slowing with preponderant distal demyelination. Unlike in CIDP, temporal dispersion and conduction block are not usually noted.[12] The sensory nerve action potentials are typically low amplitude or absent.[12]

Nerve ultrasound studies demonstrate significantly larger cervical nerve root cross-sectional area and regional nerve enlargements at the common entrapment sites of peripheral nerves in IgM anti-MAG neuropathy.[24,25] Pathologic studies of nerves show a mild loss of myelinated fibers, segmental demyelination, and deposits of IgM and complement in myelin sheets on immunofluorescence studies. Widening of myelin lamellae is noted in ultrastructural studies (**FIGURE 9-1**).[18,26]

The treatment approach in patients with IgM MAG neuropathy depends on various factors including the patient's age, nature of symptoms, progression, and severity. Supportive therapy is recommended in patients with mild symptoms not affecting daily activity and in older individuals with static or minimal progression. However, patients with progressive symptoms, including gait ataxia resulting in falls, or those who present with subacute proximal and distal

KEY POINTS

- The risk of progression of monoclonal gammopathy of undetermined significance to myeloma or another related disorder is 1% per year.
- Paraproteinemic neuropathies most commonly occur with IgM paraprotein.
- Serum immunofixation is more sensitive than serum protein electrophoresis and should be performed when a diagnosis of paraproteinemia is considered.
- IgM–myelin-associated glycoprotein (MAG) neuropathy typically manifests with slowly progressive sensory ataxia.
- Anti-MAG antibodies are present in 50% to 65% of patients with IgM neuropathy.
- Prolongation of distal latencies and a short terminal latency index are electrophysiologic hallmarks of IgM anti-MAG neuropathy.
- Patients with IgM MAG neuropathy who have progressive symptoms, including gait ataxia resulting in falls, or those who present with subacute proximal and distal weakness should be treated early before developing permanent deficits due to axonal degeneration.

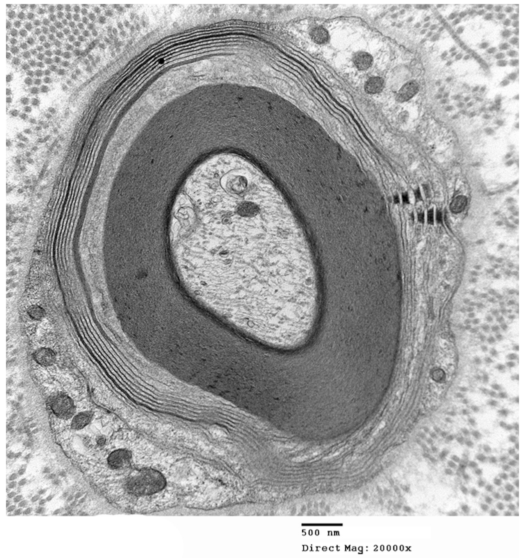

FIGURE 9-1
Typical widely spaced myelin in anti–myelin-associated glycoprotein (MAG) neuropathy. The center of the figure shows an axon, containing neurofilaments, that is surrounded by compact, tightly wrapped myelin. As one follows the myelin sheath toward the periphery of this myelinated axon, an expansion between successive layers of myelin can be seen. In anti-MAG neuropathy, this is caused by the infiltration and deposition of anti-MAG antibodies within the interperiodic space between layers of myelin. Electron micrograph, transverse section.

weakness should be treated early before developing permanent deficits due to axonal degeneration.[18]

Based on evidence implying the pathogenicity of anti-MAG antibodies, therapy has been directed at reducing circulating IgM or anti-MAG antibodies by removal (plasma exchange), modulation of the immune response (IV immunoglobulin [IVIg]), or reduction of synthesis (corticosteroids, immunosuppressive medications, cytotoxic agents, and rituximab).[13]

Two small trials suggested that IVIg may produce short-term benefits in some patients, but clinical significance and long-term effects are unknown.[27,28]

When treatment is indicated, rituximab therapy is the consensus first-line therapy. Two controlled studies of rituximab in IgM MAG neuropathy failed to demonstrate convincing benefits, not meeting the primary endpoints, although secondary endpoints and certain functional studies were positive.[29,30] Rituximab seems to help 30% to 50% of patients with IgM anti-MAG neuropathy based on two uncontrolled series.[31,32]

At least one retrospective study and several case series demonstrated a faster clinical response with the addition of chemotherapy to rituximab, suggesting potential benefits of immunochemotherapy (rituximab plus alkylating base regimens) in a subset of patients with IgM anti-MAG neuropathy and severe rapidly progressive neurologic symptoms.[33]

The newer anti–B-cell agents that cause more profound or sustained B-cell depletion are potential treatment strategies.[14] Obinutuzumab is a new-generation glycoengineered humanized anti-CD20 monoclonal antibody, which is approved for chronic lymphocytic leukemia. Rakocevic and colleagues[34] reported two cases of rituximab-nonresponsive IgM MAG neuropathy treated with obinutuzumab. These two patients showed no improvement despite normalization of the IgM level and anti-MAG antibody titers; whether this was related to axonal damage and or ineffectiveness of obinutuzumab is not clear. Briani and colleagues[35] treated two treatment-naïve patients with anti-MAG neuropathy and concurrent chronic lymphocytic leukemia with chlorambucil and obinutuzumab and observed improvement of neurologic and

neurophysiologic markers along with lowering of the IgM level and MAG antibody titers.

Selective removal of pathogenic anti-MAG antibodies by using glycopolymer has been studied mainly in animal models as a plausible antigen-specific therapy.[36] Limited evidence suggests a favorable response to first-line conventional immunomodulatory therapy for non-MAG DADS.[17]

From a hematologic standpoint, regular follow-up with serum protein electrophoresis and serum immunoelectrophoresis, along with monitoring for systemic symptoms suggestive of transformation to symptomatic Waldenström macroglobulinemia or multiple myeloma, is required.[17] CASE 9-1 is a typical example of a patient with IgM MAG neuropathy.

KEY POINT

- Electrodiagnostic features in Waldenström macroglobulinemia can be identical to IgM MAG neuropathy, but axonal or mixed axonal and demyelinating features are more common.

WALDENSTRÖM MACROGLOBULINEMIA–ASSOCIATED PERIPHERAL NEUROPATHY

Waldenström macroglobulinemia is a low-grade B-cell lymphoproliferative disorder, a lymphoplasmacytic lymphoma, characterized by 10% or greater bone marrow infiltration by lymphoplasmacytic cells and IgM monoclonal gammopathy.[10]

Clinical features are related to tumor infiltration (cytopenia, hepatomegaly, splenomegaly, lymphadenopathy), circulating IgM (hyperviscosity, cryoglobulinemia, and cold agglutinin hemolytic anemia), and tissue deposition of IgM (polyneuropathies, glomerular disease, amyloidosis).[37] About 93% to 97% of patients with Waldenström macroglobulinemia have a somatic variation in the *MYD88* gene, which codes for an adaptor protein in the B-cell receptor pathway.[38]

Neuropathy is common in patients with Waldenström macroglobulinemia.[39] The pathogenesis of the underlying neuropathy seems to be multifactorial and could be related to one of several mechanisms including anti-MAG antibodies, coexistent AL amyloidosis, type I cryoglobulinemia, vasculitis, IgM binding to unidentified peripheral nerve antigens, or, less frequently, direct tumor cell infiltration of the nerves.[10] The clinical phenotype is influenced by the pathogenic mechanisms driving the polyneuropathy.

Neuropathy symptoms are a function of the pathophysiology. When demyelinating, they are identical to IgM MAG neuropathy[40]; IgM MAG antibodies are present in 50% of the patients who have demyelinating neuropathy.[10] Electrodiagnostic features can indicate demyelination (resembling IgM MAG neuropathy or CIDP without MAG antibodies), or, more commonly, axonal loss with heterogeneous phenotypes.[40]

Treatment of patients with Waldenström macroglobulinemia, which should be under the supervision of a hematologist, depends on the hematologic parameters and systemic and hyperviscosity symptoms. The choice of primary therapy is based on a patient's gene variation profile, disease-related features, comorbid conditions, and toxicity profile. Chemoimmunotherapy (dexamethasone, rituximab and cyclophosphamide, and bendamustine-rituximab) or Bruton tyrosine kinase therapies represent the two most used approaches in Waldenström macroglobulinemia.[38] Autologous stem cell transplantation should be considered in select patients.[38,41] Generally, a bortezomib-based regimen should be avoided in patients with peripheral polyneuropathy.

Apart from symptomatic treatment of the neuropathy, initiation of systemic chemoimmunotherapy to treat the underlying hematologic derangement can potentially improve the neuropathy associated with Waldenström macroglobulinemia.[42]

In the pivotal trial studying the role of the Bruton tyrosine kinase inhibitor ibrutinib in relapsed or refractory Waldenström macroglobulinemia for progressive rituximab-nonresponsive peripheral sensory neuropathy, nine patients (14%) received ibrutinib; five patients had subjective neuropathy improvement, and neuropathic symptoms remained stable in four patients during the treatment course. However, these results should be interpreted with caution, because the study lacked the objective parameters to assess neuropathy improvement or stabilization.[43]

A transient increase of serum IgM (IgM flare) occurs in 30% to 80% of patients treated with rituximab-based therapies, which may exacerbate IgM-related complications including polyneuropathy, for which therapeutic plasma exchange could be used as a concurrent temporizing measure.[42] Plasma exchange with the

CASE 9-1

A 73-year-old man was referred by his primary neurologist for neuropathy evaluation. He presented with a 3-year history of progressive distal sensory symptoms and imbalance. He was found to have an IgM kappa monoclonal gammopathy after 3 years of symptoms. His hematologist diagnosed him with monoclonal gammopathy of undetermined significance (MGUS) because additional hematologic workup was unrevealing. He was diagnosed by his primary neurologist as having chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and was started on IV immunoglobulin (IVIg). Initially, it was thought his numbness decreased, but the improvement was arrested despite adjusting the IVIg dose and frequency.

At the time of the initial neuromuscular consultation, he was noted to have decreased sensation affecting large more than small fiber modalities in a length-dependent pattern with sensory ataxia, a positive Romberg sign, and intact strength.

Motor nerve conduction studies, shown in the table, demonstrated the presence of a severe demyelinating motor neuropathy with distal preponderance, manifested as short terminal latency index. There was no conduction block or temporal dispersion.

His myelin-associated glycoprotein (MAG) antibody level was elevated at 19,000 Bühlmann titer units (BTU) with confirmed positive Western blotting.

His serum IgM level was 362 mg/dL (normal range, 40 to 130 mg/dL). After discussion, the decision was made to treat him with rituximab. He had mild to moderate improvement in sensory symptoms after one cycle of treatment (375 mg/m^2 weekly for 4 weeks), but his response seemed to plateau, and he did not have further neurologic improvement with two additional treatment cycles. On his last evaluation, the decision was made to monitor him clinically while continuing neurorehabilitation.

aim to remove pathogenic monoclonal components should also be considered in patients with acute neurologic deterioration.[44]

CRYOGLOBULINEMIA

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than normal body temperature (<37°C [98.6°F]) and redissolve on rewarming.[45] In type I cryoglobulinemia, the cryoglobulins are monoclonal immunoglobulins (in descending order of likelihood: IgM, IgG, IgA, and light chain). It develops in the setting of monoclonal gammopathies.[45] Forty percent of cases have MGUS, and the remaining 60% have B-cell lineage malignancy (eg, multiple myeloma, Waldenström macroglobulinemia, or chronic lymphocytic leukemia).[45] Type II is a mixed cryoglobulinemia and is usually associated with hepatitis C virus infection but may occur in lymphoproliferative disorders as well.

Peripheral neuropathy can be seen in about 30% of cases.[45] It usually manifests as a painful sensory neuropathy affecting predominantly small

Nerve and site	Latency (ms)	Amplitude (mV)	Conduction melocity (m/s)
Peroneal (left)			
Ankle	9.0 (normal, <6.4)	4.7 (normal, >2.2)	Terminal latency index: 0.26 (normal, >0.36)
Fibular head	18.2	3.6	34 (normal, >40)
Tibial (left)			
Ankle	13.0 (normal, <5.8)	2.3 (normal, >4.0)	Terminal latency index: 0.23 (normal, >0.35)
Popliteal fossa	30.8	1.3	26 (normal, >40)
Median (left)			
Wrist	7.3 (normal, <4.4)	6.0 (normal, >5.0)	Terminal latency index: 0.20 (normal, >0.32)
Elbow	12.4	6.0	46 (normal, >50)

COMMENT

This case illustrates the importance of concurrent neurologic and hematologic phenotyping to ensure appropriate diagnosis and management. Diagnosis of IgM MAG-associated neuropathy should be considered in all patients with an IgM monoclonal protein and demyelinating neuropathy, particularly in those with distal demyelination. In patients with progressive symptoms, rituximab treatment should be considered, but it is not clinically effective in all patients.

KEY POINTS

- Although nerve biopsy continues to be the gold standard test for the diagnosis of neurolymphomatosis, neuroimaging and positron emission tomography (PET) increase diagnostic yield.

- CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies) and CANDA (chronic ataxic neuropathy with anti-disialosyl IgM antibodies) are rare sensory ataxic neuropathies associated with disialosyl antibodies, monoclonal proteins, and cold agglutinins characterized by chronic neuropathy with sensory ataxia, areflexia, and motor weakness occasionally involving the ocular motor and bulbar muscles.

- In patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and an IgG or IgA monoclonal gammopathy, the paraprotein is considered to be coincidental and not causative.

fibers, sparing autonomic nerves, or as mononeuritis multiplex (ie, vasculitic neuropathy).[46] Early recognition of cryoglobulinemia is essential to diagnose and treat any underlying or associated systemic or hematologic condition.

NEUROLYMPHOMATOSIS

Neurolymphomatosis is a rare manifestation of non-Hodgkin lymphoma and leukemia characterized by direct malignant lymphocytic invasion of the peripheral nervous system.[47]

It can affect cranial nerves, peripheral nerves, and nerve roots or plexus, and thus, the clinical picture is extremely heterogeneous presenting with neuropathies, painful radiculopathies, cranial neuropathies, mononeuropathies, and polyradiculopathies.[14]

Neurolymphomatosis should, therefore, be considered in all patients with lymphoma with unexplained peripheral nervous system dysfunction (polyneuropathy, mononeuropathy, or radiculopathy) or in patients with severe pain with an asymmetric distribution and rapid progression of neurologic symptoms.[14]

Nerve biopsy is the gold standard test for the diagnosis of neurolymphomatosis, but neuroimaging and PET-CT have greatly contributed to the diagnostic yield.[48] According to the International Primary Central Nervous System Lymphoma Collaborative Group report, the diagnostic yield of MRI and PET-CT is high, with abnormal findings found in 77% and 84%, respectively.[49] CSF studies show elevated protein, low glucose, and elevated white blood cell counts in most patients.[14] However, in the International Primary Central Nervous System Lymphoma Collaborative Group study, malignant cells and suspicious cytology were reported only in 40% and 13% of cases, respectively.[49] CSF flow cytometry must be used to confirm the diagnosis.[14] The prognosis of neurolymphomatosis is poor, but early diagnosis and aggressive therapy can help prevent neurologic deterioration and are associated with a prolonged survival in a subset of patients.[49]

CANOMAD AND CANDA

CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies) and CANDA (chronic ataxic neuropathy with antidisialosyl IgM antibodies) are rare sensory ataxic neuropathies associated with disialosyl antibodies, monoclonal proteins, and cold agglutinins characterized by chronic neuropathy with sensory ataxia, areflexia, and motor weakness occasionally involving the ocular motor and bulbar muscles.[48,50] The exact pathogenesis of these syndromes is not fully understood, but evidence suggests that direct damage to dorsal root ganglia underlies most of the morbidity seen in these disorders.[48]

The largest retrospective study of CANOMAD revealed that one-third of the patients had an overt hematologic malignancy, mainly Waldenström macroglobulinemia.[50] Acquired demyelinating features are common findings on electrodiagnostic studies, but pure axonal polyneuropathy may also be seen.[48,50] Nerve ultrasound studies of four patients with CANOMAD demonstrated features of an acquired demyelinating polyneuropathy in all patients, including one patient with axonal features on electrodiagnostic testing.[48]

IVIg and rituximab-based regimens were the most effective therapies in one large, multicenter, retrospective study.[50] Rituximab was most effective at halting the disease progression in eight of nine patients treated in another retrospective study; IVIg prevented relapses in approximately half of the treated patients in this cohort.[48]

IGA AND IGG PARAPROTEINEMIC NEUROPATHIES

Although these monoclonal gammopathies can be noted during the workup of patients with polyneuropathy, a definite causal relationship between non-IgM monoclonal proteins and peripheral neuropathy may not be established, except in patients with POEMS syndrome or AL amyloidosis.[6,7] IgG- and IgA-associated CIDP is labeled as *CIDP with a coincidental paraprotein*, with 80% of these patients having a response to conventional CIDP therapy.[12]

POEMS SYNDROME

POEMS syndrome is a rare multiorgan paraneoplastic disorder associated with plasma cell dyscrasia. This acronym refers to several, but not all, of the features of the syndrome.[51]

The pathogenesis of POEMS syndrome is not well understood but is likely related to cytokine imbalance outlined by excessive production of multiple proinflammatory and angiogenic cytokines, including but not limited to vascular endothelial growth factor (VEGF).[52]

Diagnosis relies on satisfaction of both major and minor criteria (TABLE 9-4)[53]; polyneuropathy and the presence of the monoclonal plasma cell are mandatory.

Criteria for the Diagnosis of POEMS Syndrome

TABLE 9-4

Mandatory criteria

- Polyneuropathy (typically demyelinating)
- Monoclonal plasma cell–proliferative disorder (almost always lambda light chain)

Major criteria (one required)

- Castleman disease (lymphoproliferative disease with angiofollicular lymph node hyperplasia)
- Sclerotic bone lesions
- Vascular endothelial growth factor (VEGF) elevation

Minor criteria (one required)

- Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
- Extravascular volume overload (edema, pleural effusion, or ascites)
- Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, or pancreatic)
- Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, or white nails)
- Papilledema
- Thrombocytosis or polycythemia

POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes.

Electrodiagnostic studies usually show a prominent demyelinating neuropathy with secondary axonal loss and characteristic patterns that are helpful for early diagnosis and distinction from CIDP. Despite the presence of conduction velocity slowing in both CIDP and POEMS syndrome, certain features may help differentiate the two: (1) conduction block is much less frequent in POEMS syndrome; (2) demyelination in POEMS syndrome is more uniform, and conduction slowing is prominent in the intermediate nerve segments, as opposed to multifocal demyelination involving distal and proximal nerve segments in CIDP; (3) CMAPs and sensory nerve action potentials (SNAPs) of the lower limbs are disproportionally more severely affected in POEMS syndrome compared with CIDP (CMAP amplitude is more attenuated in the lower limbs than in the upper limbs in POEMS syndrome); and (4) axonal loss is more prominent in POEMS syndrome than in CIDP.[54]

Nerve ultrasound studies of 34 patients with POEMS syndrome demonstrated a larger upper limb nerve cross-sectional area in those patients compared with unaffected patients, and the enlargement was more prominent proximally.[51] Nerve biopsy in POEMS syndrome reveals signs of demyelination with uncompacted myelin on electron microscopy in the absence of macrophage-associated demyelination.[55] POEMS syndrome demonstrates more axonal degeneration and epineural neovascularization, whereas CIDP has more endoneurial inflammation and onion-bulb formation.[56]

The most common type of monoclonal protein in POEMS syndrome is IgA followed by IgG, and the light chain is almost always lambda.[52,53] Serum free light chains are abnormal in at least two-thirds of patients, although the light chain ratio is normal in 80% of patients.[55]

POEMS syndrome is associated with elevated serum and plasma levels of VEGF. A plasma VEGF level greater than 200 pg/mL is highly specific for a diagnosis of POEMS syndrome in the appropriate clinical setting with 68% sensitivity and 95% specificity. The VEGF level can be falsely low if a patient was pretreated with corticosteroids. VEGF levels also correlate with the clinical response and disease activity.[57] N-terminal propeptide type I collagen has been identified as a novel marker for the diagnosis of patients with POEMS syndrome.[58]

Careful clinical and electrodiagnostic evaluations are key to an early diagnosis. The presence of thrombocytosis is a characteristic laboratory finding. Screening for concurrent endocrinopathy is indicated and includes testing serum testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, thyroid-stimulating hormone (TSH), free thyroxine, fasting glucose, cortisol, and adrenocorticotropic hormone (ACTH).

Unfortunately, delays in diagnosis are common, and patients are often misdiagnosed with CIDP and treated aggressively with unhelpful treatments such as IVIg.[59] This is a point well demonstrated in **CASE 9-2**. POEMS syndrome should be considered in all cases of refractory CIDP.

The treatment approach is determined in collaboration with a hematologist and depends on the presence of marrow plasma cell infiltration and the number of bone lesions seen on imaging studies.[52] In patients with one to three bone lesions and no clonal plasma cells detected by bone marrow biopsy, radiation therapy is a preferred strategy with generally excellent clinical responses. Patients with POEMS syndrome who have more than three bone lesions or marrow involvement by clonal plasma cells should receive systemic therapy.[52]

High-dose melphalan followed by autologous hematopoietic cell transplantation is an effective therapy for eligible patients,[52] resulting in good hematologic control, neurologic response, and survival.[55] However, patients with advanced disease are not eligible for hematopoietic cell transplantation.[55]

Immunomodulatory drugs, such as daratumumab, and proteasome inhibitors, such as bortezomib, have been used for patients who are not candidates for hematopoietic cell transplantation.[52,55] Lenalidomide (a derivative of thalidomide) has been shown to be a highly effective and safe therapy.[60] Anti-VEGF therapies, such as bevacizumab, that lead to undetectable VEGF levels have not demonstrated consistent clinical benefit.[52] Neurologic response can be delayed and incomplete and may take up to 6 to 36 months after completion of therapy.[52]

AMYLOID LIGHT CHAIN NEUROPATHY

AL amyloidosis is the most common form of systemic amyloidosis in the United States, with an estimated prevalence of 2.5 per 100,000.[61] AL amyloidosis is caused by disorders of plasma cells or, rarely, B cells that produce light chain immunoglobulins with the potential for misfolding and deposition as amyloid fibrils. Amyloid fibrils gradually accumulate in multiple organs including the heart, kidneys, peripheral nerves, liver, gastrointestinal tract, and soft tissues, interfering with their structure and function.[61]

Peripheral neuropathy occurs in 17% to 36% of patients with AL amyloidosis.[61,62] It usually presents with a length-dependent sensory predominant polyneuropathy with a predilection for small fibers at the initial stage.[51] Autonomic symptoms, including orthostatic hypotension, sweating abnormalities, postprandial fullness, diarrhea, constipation, erectile dysfunction, or urinary retention, are common.[62] CASE 9-3 demonstrates some of those features.

Clinical findings of periorbital or facial purpura, hepatomegaly, and macroglossia are seen in a minority of patients. Nephrotic range proteinuria, heart failure with preserved ejection fraction, and unexplained hepatomegaly should raise the concern for AL amyloidosis neuropathy.[65]

Carpal tunnel syndrome can occur in up to 21% of patients with AL amyloidosis.[61] Involvement of the cranial nerves, lumbosacral roots, and lumbosacral plexus may occur.[62]

Nerve conduction studies are generally consistent with a length-dependent sensorimotor axonal neuropathy, but coexisting demyelinating findings (prolonged distal motor latencies, severely reduced nerve conduction velocities, abnormal temporal dispersion, prolonged F-wave latencies) are common. Rarely, definitive demyelinating features are present, fulfilling electrophysiologic criteria for CIDP.[62,66] Large fiber neuropathy becomes more overt as the disease progresses.

Serum and urine protein immunofixation electrophoresis and serum free light chains assays should be obtained in all patients suspected of amyloid neuropathy. The lambda light chain is more common than the kappa light chain in AL amyloidosis.[61]

Histopathology demonstrating amyloid deposition in tissue is required for definite diagnosis (FIGURE 9-3).[61] In general, abdominal fat aspirate is preferred over nerve biopsy because of the more favorable safety profile, despite lower

KEY POINTS

- The monoclonal gammopathy in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome is almost always the lambda type.
- A plasma vascular endothelial growth factor (VEGF) level greater than 200 pg/mL is highly specific for the diagnosis of POEMS syndrome in the appropriate clinical setting.
- Screening for concurrent endocrinopathy in patients with POEMS syndrome is indicated and includes testing serum testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, thyroid-stimulating hormone (TSH), free thyroxine, fasting glucose, cortisol, and adrenocorticotropic hormone (ACTH).
- POEMS syndrome should be considered in all cases of refractory CIDP.
- Patients with POEMS syndrome who have one to three bone lesions and no clonal plasma cells detected by bone marrow biopsy may undergo radiation therapy. Patients who have more than three bone lesions or marrow involvement by clonal plasma cells should receive systemic therapy.
- Light chain (AL) amyloidosis neuropathy typically manifests initially as a rapidly progressive painful sensory neuropathy with autonomic dysfunction.

CASE 9-2

A 60-year-old man was referred by his primary neurologist for a neuromuscular opinion regarding a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with a 17-month history of progressive neurologic symptoms. His initial symptoms were a painful tingling and burning sensation in the soles of his feet. This was followed by progressive weakness in his bilateral lower extremities and frequent falls. Within 10 months, he was using a wheelchair exclusively. He then noted progressive weakness and sensory symptoms in his hands. At that time, he was admitted to the hospital. CSF examination demonstrated albuminocytologic dissociation with an elevated protein of 114 mg/dL. He underwent five sessions of plasma exchange with an equivocal response. Subsequently, he was treated with IV immunoglobulin (IVIg) and additional plasma exchanges with no effect.

On initial evaluation with the neuromuscular neurologist, he reported unintentional weight loss of 18 kg (40 pounds). He was not able to write or feed himself. He confirmed progressive darkening of his skin; a vascular papule was noted on the right side of his forehead.

Neurologic examination demonstrated severe distal worse than proximal upper and lower limb weakness, muscle atrophy, areflexia, and length-dependent sensory loss to all modalities.

Electrodiagnostic studies were abnormal, revealing absent compound muscle and sensory nerve action potentials with recording at distal sites. However, compound muscle action potentials of the axillary and musculocutaneous nerves were present and revealed severely prolonged latencies.

A complete blood cell count revealed an elevated platelet count of 603,000 cells/mm^3. Serum protein electrophoresis was normal, but immunofixation demonstrated IgA lambda monoclonal protein. The quantitative IgA level was within the normal range. The vascular endothelial growth factor (VEGF) level was elevated at 360 pg/mL (normal range, 9 to 86 pg/mL). A bone marrow biopsy demonstrated 5% to 10% lambda light chain–restricted plasma cells.

A skeletal bone survey was unremarkable. Positron emission tomography (PET)-CT of his chest, abdomen, and pelvis demonstrated hepatosplenomegaly and multiple prominent lymph nodes (FIGURE 9-2). His testosterone level was 44 ng/dL (normal range, 250 to 1100 ng/dL). His forehead lesion biopsy was consistent with capillary hemangioma.

He was diagnosed with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome and started on lenalidomide and dexamethasone. His VEGF level and the immunofixation normalized. However, neurologic improvement at a 9-month follow-up was still lacking.

COMMENT

This case illustrates the significance of early diagnosis and treatment to mitigate the disability seen with neurologic progression in patients with POEMS syndrome. Key factors in recognizing the diagnosis are CIDP refractory to conventional therapy, electrodiagnostic findings of a demyelinating neuropathy with axonal loss, neuropathic pain, presence of thrombocytosis, and other systemic signs.

FIGURE 9-2
Whole-body positron emission tomography (PET)–CT of the patient in CASE 9-2. The image shows hepatosplenomegaly (*arrowheads*) and retroperitoneal lymphadenopathy (*arrow*) in a patient with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome.

sensitivity.[12] Other tissues that may be biopsied to detect amyloid include bone marrow, minor salivary glands, or skin. Amyloid subtyping should be performed, preferably with mass spectrometry, to exclude hereditary amyloidosis (eg, caused by transthyretin deposition in patients with *TTR* gene variations) although it is technically challenging and available only at specialized facilities.

AL amyloidosis can progress rapidly; hence, early diagnosis and institution of appropriate therapy are crucial. The mainstay of treatment is to address the underlying plasma cell dyscrasia. This approach is adapted from multiple myeloma treatment, which includes high-dose chemotherapy followed by stem cell transplantation in eligible patients. Combinations of daratumumab with bortezomib, cyclophosphamide, and dexamethasone are options for transplant-ineligible patients with AL amyloidosis; however, bortezomib should be avoided in patients with peripheral neuropathy. Emerging therapeutic

CASE 9-3

A 71-year-old man was referred by his primary neurologist with a diagnosis of idiopathic neuropathy. He had 10 months of progressive distal weakness, atrophy, dysesthesia, and numbness in his hands and feet. His symptoms progressed rapidly, and he needed to use a cane for ambulation. On questioning, he also reported early satiety and unintentional weight loss of 27 kg (60 lb) since the onset of symptoms. This was ascribed to a prior gastrointestinal surgery. He also had decreased exercise tolerance and dyspnea with exertion.

The examination was remarkable for significant orthostatic hypotension. Neurologic examination demonstrated distal leg weakness. His patellar reflexes were reduced, and ankle reflexes were absent. Sensory examination showed reduced pinprick and temperature sensation up to the midshin and a mild decrease in vibration sensation and proprioception in his toes. His gait revealed sensory ataxia with a positive Romberg sign.

Electrodiagnostic studies demonstrated a length-dependent axonal sensorimotor polyneuropathy. Laboratory studies demonstrated an IgG lambda monoclonal protein in the serum. Bone marrow biopsy demonstrated 5% to 10% lambda-restricted plasma cells. Congo red staining was negative in the fat aspirate but was present in the bone marrow and omental resected tissue from a prior gastrointestinal polyp surgery. He was referred for a cardiology consultation, and a cardiac MRI and pyrophosphate scan were consistent with cardiac amyloidosis. His N-terminal pro b-type natriuretic peptide (Nt-pro BNP) level was significantly elevated.

COMMENT

This case illustrates the typical neuropathy phenotype seen in light chain amyloidosis, which is characteristically a painful, rapidly progressive peripheral neuropathy with autonomic symptoms. Attention to systemic symptoms and screening all patients for autonomic symptoms or signs are crucial for early diagnosis.[63,64]

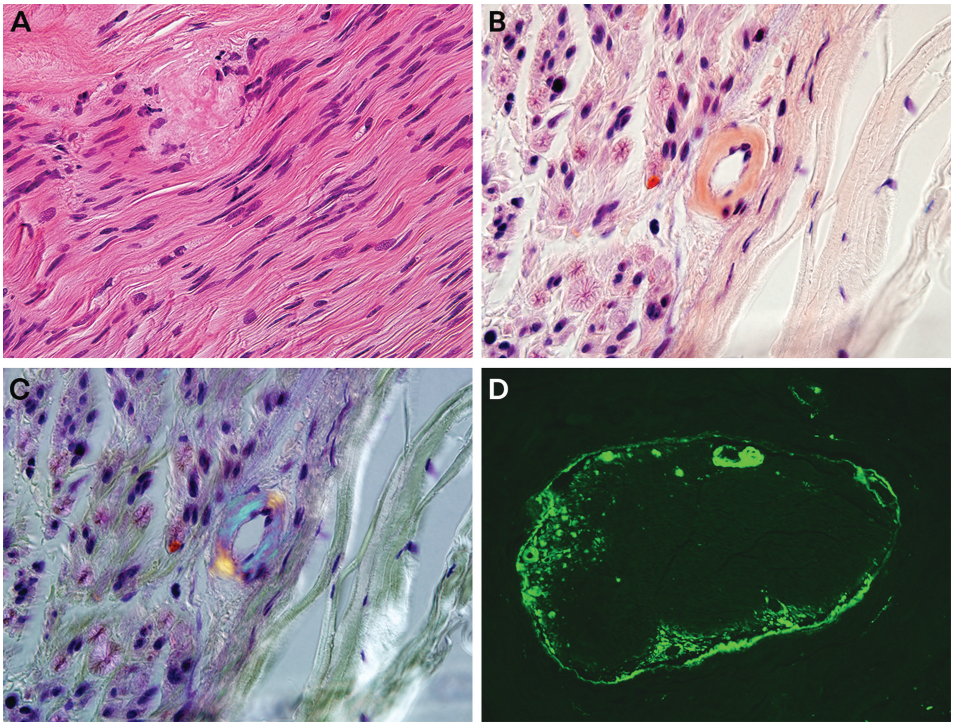

FIGURE 9-3
Sural nerve biopsy showing amyloid deposits. *A*, Hematoxylin and eosin (H&E)–stained section of a sural nerve in longitudinal section shows an ill-defined, poorly organized, eosinophilic amyloid deposit. *B*, Transverse section of a sural nerve stained with Congo red shows pink eosinophilia within the vessel walls of a small endoneurial vessel. *C*, Deposits exhibit apple-green birefringence when viewed through polarized light. *D*, Cross-section of a sural nerve shows the presence of intense Thioflavin S staining with a subperineurial distribution and staining of endoneurial vessels. Fluorescent microscopy, green filter, formalin-fixed, and paraffin-embedded.

KEY POINTS

- **In AL amyloidosis, the lambda light chain is the most common culprit.**
- **Amyloid subtyping should be performed when observed pathologically, preferably with mass spectrometry, to exclude hereditary amyloidosis (eg, caused by transthyretin deposition in patients with *TTR* gene variations).**

strategies include removing amyloid deposits and inhibiting amyloid fibril formation.[63]

MULTIPLE MYELOMA–ASSOCIATED PERIPHERAL NEUROPATHY

Multiple myeloma is a malignant non-IgM plasma cell disorder (IgG more frequently than IgA) that accounts for approximately 10% of hematologic malignancies. Peripheral neuropathy is a common complication of multiple myeloma, which can be related to the disease itself or secondary to the treatment.

Clinical and electrodiagnostic peripheral neuropathy has been reported in 7% to 54% of patients being treated for multiple myeloma,[64] but the mechanism is poorly understood. However, AL amyloidosis is accountable for 30% to 40% of neuropathies in myeloma.[67] Other potential etiologies are direct compression of nerves by plasmacytomas or bony lesions, mixed cryoglobulinemia, and cytokine-mediated injury.[68,69]

Multiple myeloma–associated peripheral neuropathy usually presents with slowly progressive, painless, length-dependent sensory or sensorimotor polyneuropathy. Although it can be demyelinating, the pathophysiology is predominantly axonal. Treatment is targeted to the underlying plasma cell dyscrasia. Neurotoxicity is a common side effect of multiple myeloma therapy, particularly related to the use of thalidomide and bortezomib, both of which can

cause polyneuropathy. These agents are associated with sensory-predominant peripheral neuropathies in 30% to 50% of patients.[68-70] Second-generation proteasome inhibitors and immunomodulatory drugs, such as carfilzomib and pomalidomide, have a lower neurotoxicity profile.

SYMPTOMATIC AND SUPPORTIVE TREATMENT STRATEGIES

Symptomatic pharmacologic treatment for painful neuropathy usually involves gabapentinoids, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors (SNRIs), and sodium channel blockers. Guidelines from the American Academy of Neurology provide evidence-based information for the treatment of painful polyneuropathy.[71] Nonpharmacologic strategies include physical and occupational therapy, orthotic devices, and rehabilitation programs.

CONCLUSION

Clinicians' awareness of the distinct neurologic and hematologic features of each paraproteinemic neuropathy is essential for early diagnosis and appropriate treatment to limit disability. It is important to define the neuropathy phenotype and determine if the monoclonal gammopathy is coincidental or related to an underlying hematologic condition. In the former, diagnostic steps and a treatment algorithm to address the peripheral neuropathy are needed, independent of the presence of MGUS. Patients with neuropathies attributed to underlying hematologic disorders require thorough general and neurologic examinations to characterize the phenotype and plan further investigations, including a hematologic evaluation. A multidisciplinary model of care and collaboration among several specialists is key to delivering comprehensive care to these patients.

Treatment of paraproteinemic peripheral neuropathies should address the underlying plasma cell dyscrasia. Significant advances have been made with new and emerging hematologic treatments.

The precise underlying pathophysiologic mechanisms of many paraproteinemic neuropathies are not yet fully understood, which will be needed to determine future targeted therapies. In addition, developing and validating sensitive scales and biological markers will help anticipate and monitor treatment in the future.

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DISCLOSURE

Continued from page 1492

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REVIEW ARTICLE

Hereditary Neuropathies

By Leslie H. Hayes, MD; Reza Sadjadi, MD

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

SUPPLEMENTAL DIGITAL CONTENT (SDC) AVAILABLE ONLINE

VIDEO CONTENT AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: This article provides an overview of hereditary neuropathies, describes the different hereditary neuropathy subtypes and the clinical approach to differentiating between them, and summarizes their clinical management.

LATEST DEVELOPMENTS: Increasingly available clinical genetic testing has broadened the clinical spectrum of hereditary neuropathy subtypes and demonstrated a significant overlap of phenotypes associated with a single gene. New subtypes such as *SORD*-related neuropathy and CANVAS (cerebellar ataxia, neuropathy, vestibular areflexia syndrome) have emerged. The optimization of clinical management has improved gait and motor function in the adult and pediatric populations. Novel therapeutic approaches are entering clinical trials.

ESSENTIAL POINTS: Hereditary neuropathies constitute a spectrum of peripheral nerve disorders with variable degrees of motor and sensory symptoms, patterns of involvement, and clinical courses.

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Address correspondence to Dr Reza Sadjadi, 165 Cambridge St, Ste 820, Boston, MA 02114, rseyedsadjadi@mgh.harvard.edu.

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INTRODUCTION

Hereditary neuropathies are groups of genetically and phenotypically heterogeneous neuropathies with varying degrees of motor and sensory manifestations. The most common group of heredofamilial neuropathies is Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathies. The global prevalence of CMT is estimated to range from 10 to 30 per 100,000 people, making it the most common inherited neuromuscular condition.[1] A 2021 study suggests a rising trend in prevalence compared with earlier studies.[2]

CLASSIFICATION

Hereditary neuropathy phenotypes were initially defined based on their clinical features, specifically the degree of motor versus sensory involvement. CMT is the most common phenotype, affecting both sensory and motor modalities. Conventionally, autosomal dominant CMT is categorized into two major groups based on neurophysiology: primarily demyelinating features (CMT type 1 [CMT1]) and primarily axonal features (CMT2). Autosomal recessive inheritance is categorized as CMT4. Less common CMT types, such as CMT3 and CMT5 through CMT7, are now referred to by gene type. Magy and colleagues[3] proposed naming subtypes by electrophysiologic features, inheritance pattern, and for more than one-half of the patients with a clinical diagnosis of CMT, a genetic cause is confirmed. Five subtypes account for 90% of the diagnoses:

CMT1A due to *PMP22* duplication,[1] CMT1X due to *GJB1* variations, CMT2A due to *MFN2* variations, CMT1B due to *MPZ* variations, and hereditary neuropathy with liability to pressure palsies (HNPP) due to *PMP22* deletion.[4] For a comprehensive list of hereditary neuropathy genes and corresponding phenotypes, see Supplementary Digital Content Table 1, links.lww.com/CONT/A398.

Supplemental Digital Content

Distal hereditary motor neuropathies present with muscle weakness and atrophy without prominent sensory deficits. Compared with more common motor neuron disorders such as sporadic or genetic (*SOD1*, *C9orf72*) amyotrophic lateral sclerosis (ALS), distal hereditary motor neuropathies manifest with predominantly symmetric distal weakness greater than proximal weakness and with less prominent upper motor neuron involvement. Hereditary sensory and autonomic neuropathies (HSAN) have more prominent sensory and autonomic involvement with a relatively broad spectrum of motor involvement. There are also overlap syndromes with both central and peripheral nervous system manifestations, such as the spinocerebellar ataxias and hereditary spastic paraplegias.

CORE CLINICAL FEATURES

Clinicians should suspect hereditary neuropathies in patients with chronic distal-predominant motor or sensory deficits, diminished reflexes, and foot deformity, particularly when there is a family history of neuropathy. Depending on the clinical presentation and family history, clinicians can perform further evaluations, including electrodiagnostic evaluation and genetic testing, to characterize the hereditary process.

CMT is a chronic, slowly progressive generalized length-dependent symmetric polyneuropathy with predominantly distal motor weakness and atrophy more than distal sensory loss. A hallmark clinical feature of CMT is the distinct foot morphology characterized by pes cavus and hammer toes that result from chronic atrophy of the intrinsic foot muscles (**FIGURE 10-1**). High arches accompanied by an inward turning of the heel is referred to as a cavovarus deformity. Similar foot deformities may also occur in the setting of acquired chronic neuropathies and central processes such as cerebral palsy.

The age of symptom onset varies from early childhood through late adulthood. In general, autosomal recessive CMT manifests early, from birth through childhood.[5] Patients with dominant forms of CMT generally present later; patients with CMT1 typically develop weakness in childhood through early adulthood, whereas patients with CMT2 may have early-adult–onset or late-adult–onset symptoms. In all forms of CMT, the age of presentation for neurologic care is often many years after symptom onset.[6] Most patients have difficulty walking due to distal and proximal lower extremity weakness and sensory ataxia (**VIDEO 10-1**). They often require assistance with ambulation, ranging from shoe inserts and orthotics to unilateral or bilateral walking aids and wheelchairs. Certain hereditary neuropathies, mainly autosomal recessive forms, may have a more rapidly progressive course.[7] These cases may mimic acquired neuropathies such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), especially in pediatric populations.[8] Some hereditary neuropathies are associated with other symptoms or systemic involvement (eg, optic neuropathy in association with certain *MFN2* variations, nephropathy in patients with *INF2* variations, and central nervous system

KEY POINTS

- Charcot-Marie-Tooth (CMT) is the most common hereditary neuropathy and is usually characterized by distal motor loss greater than sensory loss, areflexia, and foot deformity.
- In general, autosomal recessive CMT manifests early, from birth through childhood.
- Patients with CMT1 typically develop weakness in childhood through early adulthood, whereas patients with CMT2 may have early-adult–onset or late-adult–onset symptoms.

FIGURE 10-1
Examples of the characteristic foot morphology in Charcot-Marie-Tooth disease (CMT). *A,* Distinctive foot morphology of high arches (*arrow*) and hammer toes (*closed arrowhead*) in a patient with Charcot-Marie-Tooth disease type 1A (CMT1A). *B,* More prominent foot deformity (high arches [*arrow*] and hammer toes [*closed arrowhead*]) and callus formation (*open arrowhead*) in a patient with CMTX1. Structural foot changes are more evident while the patient is sitting. *C and D,* A patient with axonal CMT with high arches (*C*, *arrow*) and hammer toes (*D*, *closed arrowhead*). *E,* X-ray from a patient with CMT.

involvement in some *GJB1* variations). Hearing loss is fairly common in most types of CMT.[9,10] Respiratory or bulbar symptoms may rarely occur in some subtypes.[11]

DIAGNOSTIC APPROACH

Once there is a clinical suspicion for a hereditary neuropathy, the authors of this article recommend additional testing to further characterize and subtype the neuropathy. Electrophysiology is typically the first step in the diagnostic classification to confirm the presence of a neuropathy and subtype it. However, genetic testing may be performed before electrodiagnostic testing in scenarios with a clear family history or a characteristic phenotype. In these cases, electrodiagnosis is often considered if the genetic testing is inconclusive.

Ancillary Testing

Electrodiagnostic testing can help confirm and characterize an underlying polyneuropathy and guide further evaluation. It can differentiate between distal

myopathies and sensorimotor, sensory, or motor neuropathies. Additionally, electrodiagnostic testing will determine if the polyneuropathy is primarily demyelinating or axonal. Specific electrodiagnostic features may also be seen in the context of certain neuropathy subtypes. For example, prolonged distal motor latencies and conduction block at sites prone to nerve compression is a distinct pattern seen in HNPP.

Clinicians are increasingly using ultrasonography as a diagnostic tool to assess neuropathies. Nerve cross-sectional areas are often enlarged in proximal and distal sites in common hereditary demyelinating neuropathies.[12,13] Children have smaller nerve cross-sectional areas, but compared with age-matched controls, pediatric patients with CMT1A demonstrate nerve enlargement. Ultrasonography may be a useful screening tool in the pediatric population and in situations where electrodiagnostic testing is not feasible. Clinicians rarely perform a nerve biopsy in the diagnostic evaluation of hereditary neuropathy. If performed, it is typically used to exclude alternative diagnoses such as vasculitis or infiltrative processes.[14]

Genetic Testing

Following a thorough evaluation of family history, the ordering clinician should have a thoughtful and informed discussion with the patient regarding the reasons for undergoing genetic testing. In most cases, disease-modifying therapy is not available; however, there are other compelling reasons for the patient to understand a potential genetic etiology. A more specific diagnosis may inform prognosis or allow for screening of anticipated symptoms. The results of the genetic test may impact family planning. When alternative acquired neuropathies, such as immune-mediated disorders, are being considered, a confirmed genetic diagnosis would spare the patient further unnecessary interventions and ineffective therapy. Clinicians should also discuss the sensitivity of genetic testing because negative testing does not exclude the possibility of a hereditary neuropathy.

The specific testing approach may vary depending on the clinical context. Single-gene testing of *PMP22* that looks for deletions causing HNPP or duplications associated with CMT1A may be appropriate in the correct clinical context where the patient's personal history, examination, family history, and electrodiagnostic testing strongly suggest one of these two disorders. Clinicians may use targeted-panel tests for more than 200 known neuropathy genes when the specific subtype is uncertain. If the genetic cause is not identified through the above methods, clinicians can consider more comprehensive genomic testing, either whole-exome sequencing or whole-genome sequencing. This approach allows for a nontargeted evaluation of the patient's genes. These tests may be particularly helpful in cases where the peripheral neuropathy phenotype is unclear or when there may be an overlapping syndrome. Comprehensive genomic testing is most useful when analyzed with parental samples. In the case of a family with multiple affected individuals, sequencing of the affected and unaffected family members may yield a novel variant or gene. Whole-exome sequencing may miss large deletions, duplications (eg, *PMP22* duplication for CMT1A), intronic variants, and trinucleotide repeats. Genetic counselors should be engaged early on due to the complexities of genetic testing and interpretation. In younger children with a family history where electrodiagnostic testing is not feasible, it may be appropriate to start with genetic testing.

KEY POINTS

- **Less common subtypes of hereditary neuropathies include distal hereditary motor neuropathy, a motor-predominant neuropathy, and hereditary sensory and autonomic neuropathy, a sensory-predominant neuropathy.**
- **Electrodiagnostic testing can help confirm the presence of a neuropathy and distinguish between different subtypes of hereditary neuropathy.**
- **Negative genetic testing does not exclude a hereditary neuropathy.**
- **Genetic testing for hereditary neuropathy requires a stepwise approach that may include single-gene targeted testing, a gene panel, or whole-exome or whole-genome sequencing.**
- **In the pediatric population, it may be appropriate to pursue genetic testing prior to electrodiagnostic evaluation.**

PEDIATRIC CONSIDERATIONS

One-third of patients with CMT present in infancy or childhood.[4] Early-onset severe CMT forms were initially referred to as congenital hypomyelinating neuropathy (neonatal onset) or Dejerine-Sottas syndrome (infantile onset). In the earliest-onset and most severe cases, neonates are hypotonic with global weakness and areflexia and have early swallowing and respiratory dysfunction.[15]

As in adults, the initial step in diagnosis is a thorough clinical and family history and neurologic examination. In infants and toddlers with a more insidious onset, early signs of neuropathy may include toe walking and delayed motor development, particularly in the setting of normal cognitive and language development. Often, affected children are described as clumsy and fall frequently. Patients may have an upper extremity postural tremor. In some cases of childhood-onset CMT, the weakness may not be apparent until the teenage or early-adult years, but other signs of CMT, such as the typical foot morphology and frequent ankle sprains, may be present earlier.

Accurate assessment of proximal and distal weakness in pediatric patients relies heavily on an indirect assessment of patients' gait and motor function. Muscle stretch reflexes may still be present in many children with CMT. Similarly, the sensory examination may be normal or unreliable. Therefore, brief neurophysiologic testing has diagnostic value, especially in demyelinating neuropathies after 2 years of age, when peripheral myelination is almost within the adult normative range. For example, variations in *MPZ*, *PMP22,* and *EGR2* are most common when motor velocities are very slow (<15 meters per second).[15]

Management in affected children is mainly supportive. In young children, age-appropriate activities such as outdoor play, swimming, and dance may be more feasible and appropriate than physical therapy or a specific exercise routine. Early intervention programs and focused functional occupational and physical therapy are important to help children and families build compensatory habits that improve gait and function and reduce the risk of injuries. Ground reaction ankle-foot orthoses can help improve gait efficiency and reduce fall risk (VIDEO 10-2). Additionally, some patients might consider nighttime bracing to provide passive stretch and help prevent early contractures. Orthopedic care should be part of a multidisciplinary approach to management. Triple arthrodesis, or surgical fusion of the subtalar, talonavicular, and calcaneocuboid joints in the feet, is not recommended for children.[16]

DEMYELINATING CHARCOT-MARIE-TOOTH DISEASE

CMT1 is distinguished from other forms of CMT by the electrophysiologic findings of motor nerve conduction velocities less than 38 meters per second in the upper extremity.[17] CMT1A is the most common form of CMT, accounting for 37% of all CMT and 55% of genetically confirmed CMT.[18] CMT1A is an autosomal dominant disorder primarily caused by a 1.5-Mb duplication on chromosome 17p11.2, which leads to a three-copy duplication of the *PMP22* gene. *PMP22* encodes peripheral myelin protein 22, a structural protein in the myelin sheath (FIGURE 10-2[19]).[20] CMT1A is the prototypical CMT phenotype with onset in the first two decades of life. Early symptoms are often falling or tripping and footdrop. Foot deformity with pes cavus and hammer toes is a distinctive feature (FIGURE 10-1), occurring in up to 90% of patients.[6] The foot morphology

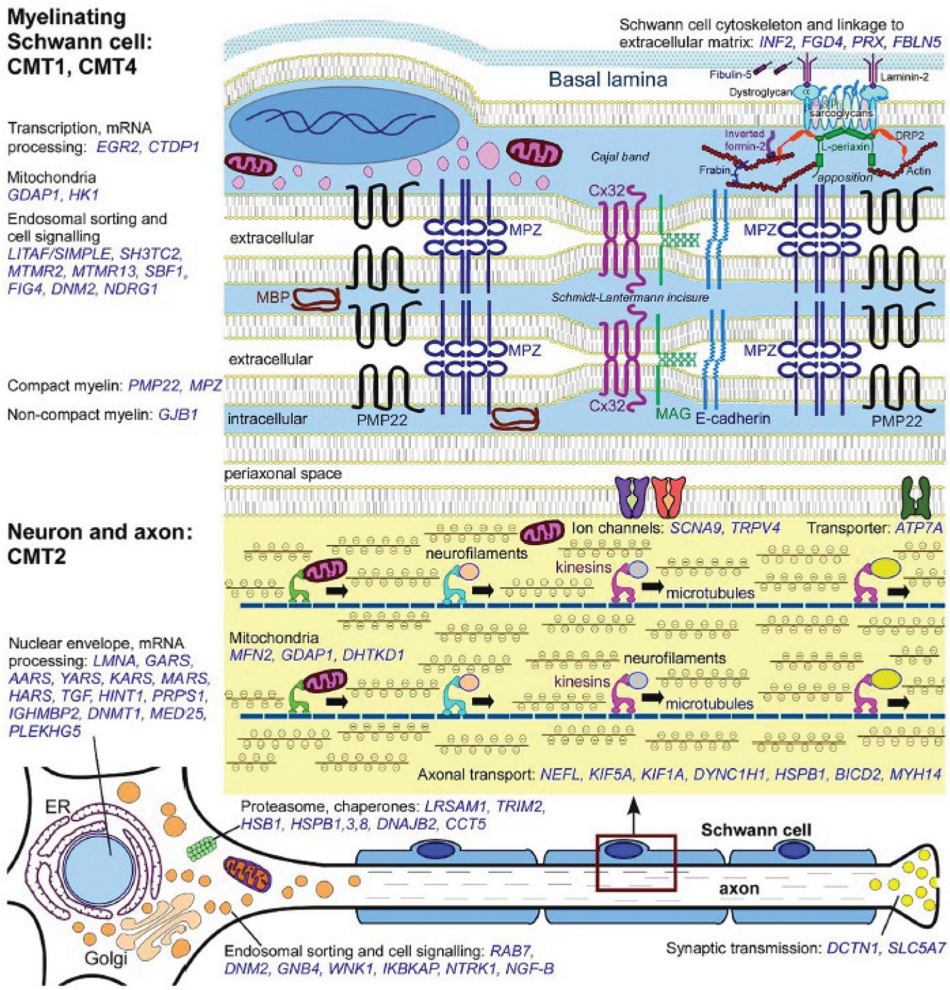

FIGURE 10-2

Charcot-Marie-Tooth disease (CMT) genes and mechanisms.

Cx32 = Connexin 32; DRP2 = dystrophin-related protein 2; ER = endoplasmic reticulum; MAG = myelin-associated glycoprotein; MBP = myelin basic protein; MPZ = myelin protein zero; mRNA = messenger ribonucleic acid; PMP22 = peripheral myelin protein 22.

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often precedes clinically apparent weakness, and these patients are frequently first evaluated by orthopedists. Their legs may appear tapered due to atrophy and can be described as having an "inverted champagne bottle" or "stork leg" appearance. Affected patients occasionally have proximal weakness, particularly of knee extension.[6] As the disease progresses, patients may become aware of intrinsic hand weakness and atrophy. Areflexia, particularly in the lower extremities, is common but not universal. Sensory loss affects both small and large fibers with a stocking-glove distribution. Pain and fatigue are also common symptoms and can significantly impact patients' quality of life (CASE 10-1).[21]

There are some atypical presentations of CMT1A, such as hypotonia in infants[15] or late-adult–onset CMT1A.[22] There are small case series of additional features such as sensorineural hearing deficits[9] and vestibular impairment.[23] Auditory dysfunction may be of particular concern in pediatric patients, given

KEY POINTS

- One-third of patients with CMT present in infancy or childhood.
- History of clumsiness or frequent falling can be an early sign of a hereditary neuropathy in the pediatric population.
- Autosomal dominant CMT1A is the most common CMT and has a prototypical phenotype characterized by childhood- to early-adult–onset distal motor weakness, sensory loss, areflexia, and foot deformity.
- Some patients have a demyelinating CMT that can clinically and electrophysiologically mimic chronic inflammatory demyelinating polyradiculoneuropathy.
- Sorbitol dehydrogenase deficiency (SORD-CMT) is a recently discovered autosomal recessive axonal neuropathy with distinctive early plantar flexion weakness.
- CMTX1 is the second-most common CMT subtype, and it may present with episodes of transient neurologic symptoms with white matter abnormalities.

the potential impact on speech and language development.[9,24] Respiration is largely unaffected; however, some patients may have phrenic nerve involvement that leads to hypoventilation.[25] There also appears to be an increased prevalence of obstructive sleep apnea in patients with CMT1 (37%), although the causal relationship is unclear.[26] While not a common or prominent manifestation, there are some case reports of patients with CMT1A exhibiting central nervous system involvement, such as demyelinating lesions, decreased white matter volume on imaging, or cognitive disorders.[27-29]

CMT1B is caused by heterozygous variations in *MPZ*, which encodes a transmembrane protein involved in the adhesion of myelin layers around nerve axons (FIGURE 10-2).[30] Typically CMT1B is clinically and electrophysiologically similar to CMT1A; however, *MPZ* variations can also cause an intermediate phenotype or a later-onset axonal CMT (CMT2J).[30] Additional CMT1 subtypes are autosomal dominant and include CMT1C caused by *LITAF* variations, CMT1D caused by *EGR2* variations, CMT1E caused by point variations in

CASE 10-1

A 20-year-old man presented with gait disturbance. He reported a normal developmental history except for difficulty running like other children and frequent ankle spraining in adolescence. As he got older, he noticed numbness in his toes and developed more significant foot deformity and imbalance. His family history revealed similar symptoms in his brother and father.

He had distinct foot morphology in the form of high arches and hammering of the toes. Strength was 4/5 for finger abduction, ankle dorsiflexion, and foot eversion. Muscle stretch reflexes were unobtainable. He had gradient sensory loss to pinprick at the midfoot, and vibration testing using a Rydel-Seiffer tuning fork was 0/8, 7/8, and 8/8 at his great toes, medial malleoli, and knees, respectively. He had a prominent steppage gait. His electrodiagnostic evaluation was notable for the uniform slowing of motor conduction velocities with a median motor velocity of 17.8 meters per second.

His genetic testing was positive for the duplication of *PMP22*, which is consistent with CMT1A.

Sensory and motor nerve conduction study results are shown in the tables:

Sensory nerve and sites	Distance, cm	Peak latency, ms	Amplitude, μV
Right radial, snuffbox			
Forearm (antidromic)	10	4.4	4.9
Right sural, lateral malleolus			
Calf (antidromic)	14	NR	NR

NR = no response.

PMP22, CMT1F caused by *NEFL* variations, and CMT1G caused by *PMP2* variations.[18]

CIDP is often on the differential diagnosis for CMT1. A retrospective study of patients with CIDP found that 3.2% of CIDP diagnoses were instead genetically confirmed CMT.[8] The misdiagnosed group had a younger age of onset, more prominent distal atrophy at presentation, and lack of response to immunotherapy. Electrophysiology can be helpful to distinguish between acquired versus hereditary forms of demyelinating polyneuropathy. However, this approach has pitfalls because some CMT subtypes (eg, *GJB1*, *FIG4*, *PCK2*) can have features of acquired demyelination such as conduction block and temporal dispersion.[31]

AXONAL CHARCOT-MARIE-TOOTH DISEASE

About 30% of genetically confirmed CMT cases are axonal, although the majority of axonal CMT cases are not genetically confirmed; the yield for genetic testing

Motor nerve and sites	Distance, cm	Latency, ms	Amplitude, mV	Velocity, m/s
Right median, abductor pollicis brevis				
Wrist	6	13.1	6.3	
Elbow	22.5	25.7	5.8	17.8
Right ulnar, abductor digiti minimi				
Wrist	6	8.5	5.6	
Below elbow	19.5	19.4	5.3	17.8
Above fibular	10	23.4	5.0	18.4
Right peroneal, tibialis anterior				
Below fibular	6	5.9	4.0	
Above fibular	9	11.5	4.0	16.1
Right peroneal, extensor digitorum brevis				
Ankle	9	NR	NR	
Right tibial, abductor hallucis				
Ankle	10	NR	NR	

NR = no response.

COMMENT

CMT1A, due to duplication of the *PMP22* gene, is the most common autosomal dominant, demyelinating hereditary neuropathy. Electrodiagnostic testing shows uniform motor slowing with conduction velocities around 20 meters per second.

for a patient with axonal neuropathy is around 20%.[4,32] Clinically, axonal and demyelinating CMT present similarly, although there are generally more patients with a later onset of axonal neuropathy. In axonal CMT, nerve conduction studies demonstrate low-amplitude motor and sensory responses with relatively preserved conduction velocities. Genes that cause CMT play a role in a range of functions in the neuron, axon, Schwann cell, and myelin. These functions include nuclear envelope processing, organelle functions, mRNA processing, membrane excitability, cytoskeletal structure, and transport.[19]

Axonal CMTs are genetically heterogeneous. Variations can be autosomal dominant or recessive. There are more than 30 genes known to cause CMT2. These CMT2 subtypes were originally named with alphabetical letters; however, there are now more genes than letters, which has prompted a shift toward gene-centered nomenclature.

MFN2-related CMT (CMT2A) is the most common autosomal dominant CMT2 subtype accounting for 3% to 4% of all CMT and 7% to 12% of genetically confirmed cases,[4,32] although it can also rarely be autosomal recessive. Mitofusin 2 plays a role in mitochondrial fusion and fission and axonal transport. Earlier symptom onset often correlates with more severe disease progression and a higher likelihood of wheelchair dependence in the future.[33] As with other CMT subtypes, distal motor weakness is common alongside sensory loss. Compared with other CMT subtypes, progression may appear more rapid in some patients.[33] In addition to the neuropathy, certain *MFN2* variations have been associated with optic atrophy, hearing loss, vocal cord paralysis, diaphragmatic weakness with hypoventilation, signs of upper motor neuron dysfunction, and cognitive impairment.[34-36] White matter abnormalities have also been described but are not a hallmark of the disease.[37]

AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH DISEASE

An autosomal recessive inheritance pattern, whether demyelinating or axonal, accounts for less than 10% of CMT.[5,18] Autosomal recessive CMT is called CMT4, is generally demyelinating, and has 11 gene subtypes (CMT4A-4J). Axonal autosomal recessive CMT forms are often grouped under CMT2. Autosomal recessive CMT usually has an earlier age of onset (infancy and childhood) and a more progressive course. In addition to the characteristic distal weakness, patients also have proximal weakness, which may lead to a loss of ambulation. For example, CMT4A caused by biallelic *GDAP1* variations presents in early childhood with distal weakness and sensory deficits that rapidly progress. The neuropathy appears mostly demyelinating but may also have mixed electrophysiologic features.[38]

One of the recently described types of autosomal recessive CMT is caused by biallelic *SORD* variations. These patients have a motor-predominant axonal neuropathy (CMT2) or exclusively motor neuropathy that typically begins during adolescence or early adulthood, progresses slowly, and is rarely severe (CASE 10-2).[39] In a distinctive feature of this neuropathy, plantar flexion appears more affected than dorsiflexion. *SORD*-CMT is likely one of the more common hereditary neuropathies based on a high allele frequency.[39] *SORD* variations lead to the reduced enzymatic activity of sorbitol dehydrogenase (SORD), which is involved in the oxidation of sorbitol to fructose. A postulated pathomechanism is the toxic accumulation of sorbitol;

CASE 10-2

An 18-year-old woman with a normal birth and early developmental history presented with a 2-year history of a slowly progressive footdrop. She did not have any sensory abnormalities. Family history was notable for similar symptoms in her older brother, but her parents were unaffected. Her strength examination was notable for 4/5 thumb abduction, 4-/5 plantar flexion, and 4-/5 foot inversion. Muscle stretch reflexes were normal throughout except where they were unobtainable at the ankles. Sensory examination was normal. Her electrodiagnostic evaluation demonstrated low-amplitude motor and sensory responses consistent with an axonal motor-predominant neuropathy. Genetic testing revealed a biallelic sorbitol dehydrogenase (*SORD*) variation.

Sensory nerve and sites	Distance, cm	Peak latency, ms	Amplitude, μV
Left radial, snuffbox			
Forearm (antidromic)	10	2.4	19.2
Left sural, lateral malleolus			
Calf (antidromic)	14	3.5	5.7

Motor nerve and sites	Distance, cm	Latency, ms	Amplitude, mV	Velocity, m/s
Left median, abductor pollicis brevis				
Wrist	6	3.2	7.2	
Elbow	21	6.2	6.8	50.0
Left peroneal, tibialis anterior				
Below fibular	6	3.8	4.3	
Above fibular	9	6.1	4.0	39.1
Left peroneal, extensor digitorum brevis				
Ankle	9	4.0	1.5	
Left tibial, abductor hallucis				
Ankle	10	NR	NR	

NR = no response.

COMMENT

Biallelic variations in *SORD* genes are likely the most frequent cause of recessive hereditary neuropathy. Most patients present with a motor-predominant neuropathy. Weaker plantar flexion on examination suggests SORD deficiency. Sensory and motor nerve conduction study results are shown in the tables, demonstrating low-amplitude lower limb motor and sensory responses with mild conduction velocity slowing.

thus, a clinical trial[40] is currently studying the effects of reducing sorbitol by using an aldolase receptor inhibitor.

Another newly reported form of autosomal recessive CMT has been identified and is caused by variations in the mitochondrial gene *PCK2*. The phenotype is a demyelinating neuropathy, with some features of acquired demyelination such as temporal dispersion and conduction block. Patients experience abnormal gait and weakness. Mouse models of the disease manifest a similar neuropathy phenotype.[41]

X-LINKED CHARCOT-MARIE-TOOTH DISEASE

X-linked CMT, both dominant and recessive, accounts for between 10% to 15% of CMT. CMTX1, an X-linked dominant condition, is the second most common CMT after CMT1A.[4] CMTX1 can occur in both males and females, but males are more severely affected. CMTX1 is caused by variations in *GJB1*, which encodes connexin 32, a gap junction protein that is highly expressed in Schwann cells and oligodendrocytes.[42] Clinically, these patients have typical distal weakness and atrophy with foot deformity and onset in adolescence. These patients often have prominent thenar muscle weakness and atrophy.

Certain variations in *GJB1* are associated with recurrent transient neurologic symptoms and reversible white matter lesions.[43] These "acute stroke–like" or "acute disseminated encephalomyelitis–like" episodes present with dysarthria, dysphagia, or limb weakness in more than 90% of cases, but they can manifest

CASE 10-3

A 14-year-old boy with genetically confirmed Charcot-Marie-Tooth disease type X1 (CMTX1; *GJB1* c.227 T>G) presented with an acute episode of left-sided weakness and left-sided facial numbness. He was treated with a course of steroids, which improved his symptoms dramatically. Brain MRI with contrast (FIGURE 10-3A) showed symmetric bilateral white matter and corpus callosum restricted diffusion with mild T2 hyperintense signal. There was no mass effect and no abnormal enhancement. He had a similar episode 4 years later while hiking at high altitude that resolved spontaneously.

His younger brother presented with left arm numbness and left-sided face drooping when he was 12 years of age. His symptoms also spontaneously improved before he received steroids. Similar to his brother, his brain MRI with contrast (FIGURE 10-3B) showed restricted diffusion and T2 hyperintensity involving the bilateral centrum semiovale and splenium of the corpus callosum. Follow-up imaging 6 months later showed interval resolution of restricted diffusion involving the bilateral centrum semiovale, with faint persistent T2 signal abnormality extending along the corticospinal tracts.

with aphasia, ataxia, diplopia, vertigo, altered mental status, and other symptoms (CASE 10-3).[43] In some cases, these attacks are the presenting symptom before the neuropathy is apparent. Imaging performed during these episodes usually shows white matter T2 hyperintensities with or without diffusion restriction, often symmetrically in the centrum semiovale and corpus callosum.[43] In most cases, these episodes resolve within hours or weeks, although there are reports of persistent symptoms.[44] Similarly, the imaging findings also typically resolve. A recent systematic review of published CMTX1 cases found that 83% of patients had a recurrent episode.[43] These episodes are postulated to be caused by dysfunction in oligodendrocytes, which also express connexin 32. Although patients are often treated with steroids because of the "acute disseminated encephalomyelitis (ADEM)–like" appearance of these white matter lesions, there is no pathophysiologic evidence supporting a mechanism of acute inflammation or data supporting the efficacy of steroids.

HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

HNPP has a distinct phenotype of episodic, multifocal mononeuropathies typically at common sites of compression. Most cases are secondary to a dominantly inherited deletion or sequence variation of *PMP22* at chromosome 17p11.2, the same gene that is duplicated in CMT1A.[21,45] The prevalence range is estimated between 7.3 and 15 per 100,000 people, making it one of the more common hereditary neuropathies.[46] Age of onset is typically in adolescence or

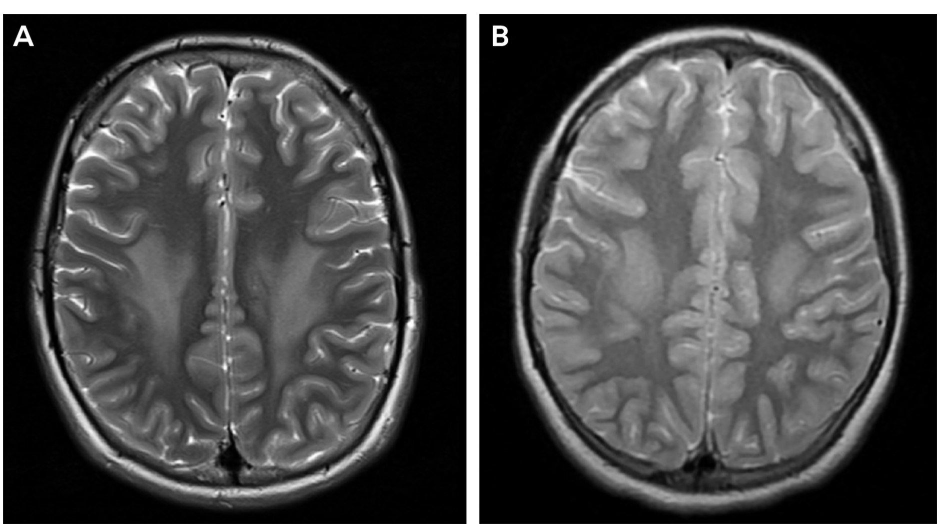

FIGURE 10-3
Brain MRI in two patients with Charcot-Marie-Tooth disease type X1. *A, B,* Axial T2-weighted images show symmetric confluent white matter hyperintensities.

COMMENT

Certain *GJB1* variations may present with acute disseminated encephalomyelitis (ADEM)-like episodes. There have been reports of central nervous system involvement in other types of CMT (eg, CMT4J).

early adulthood, but it can present at any time. Family history of an HNPP phenotype is often present.

Patients typically present with recurrent episodes of painless focal motor and sensory symptoms. There is often a history of minor compression of the affected nerve and therefore, these mononeuropathies are typically thought to be acquired in isolation. It is only when multiple episodes occur that clinicians consider the possibility of HNPP. The most common nerves affected are the peroneal (30% to 48%) and ulnar (21% to 28%) nerves, although HNPP can affect any peripheral nerve.[47,48] Brachial plexopathy occurs in approximately one-third of patients and is more common in women.[47,48] Cranial neuropathies are rare.[49,50] The symptoms and deficits from the acute attacks typically resolve within a few weeks, but residual deficits can occur. In one study, persistent motor deficits of MRC 3/5 or less at 3 months were observed in 15% of patients.[47] Patients can present with symptoms of a more generalized chronic neuropathy on examination, such as absent ankle jerks and pes cavus. Less commonly, patients with *PMP22* deletions will present with the typical CMT phenotype of slowly progressive distal weakness and atrophy.[47] There are some patients who are asymptomatic or paucisymptomatic throughout life and who may have a family member with a more typical presentation.[47,48,51]

Nerve conduction studies in patients with HNPP show focal slowing at the compression site, sometimes with a conduction block. In addition, there may be evidence of more generalized demyelination with prolonged distal motor latencies and mildly slowed motor conduction velocities. Sensory nerve action potentials may be low amplitude with prolonged distal latencies. These electrodiagnostic features are often found in affected but asymptomatic or paucisymptomatic individuals. Nerve biopsies are rarely performed but may show tomacula, which is a pathologic term describing multiple irregular myelin layers resulting in a segment of "sausage-like" hypertrophic myelin. Ultrasonography in HNPP can show enlarged cross-sectional areas at common entrapment sites, such as the ulnar nerve at the elbow, and some studies have shown enlargement at nonentrapment sites.[13,52]

Symptomatic management includes avoidance of nerve compression to help prevent episodic neuropathies. For example, these authors recommend avoiding activities like prolonged sitting, leg crossing, and leaning on one's wrist or elbows. Clinicians should make patients aware that rapid weight loss can lead to nerve compression. Clinicians often pursue surgical decompression, particularly before diagnosing HNPP, but there is no systematic evidence to support its benefit or potential harm.

The differential diagnosis of HNPP includes acquired demyelinating and multifocal neuropathies. The first few episodes of focal neuropathy are typically indistinguishable from common compression neuropathies. When episodes become recurrent, the differential diagnosis broadens to include multifocal neuropathies related to diabetes or vasculitis. Prominent pain, an associated rash, multiorgan manifestations, elevated inflammatory markers, and a more rapid and progressive disease course should prompt consideration of a vasculitic process. Inflammatory neuropathies such as typical CIDP, CIDP variants like multifocal CIDP (previously referred to as multifocal acquired demyelinating sensory and motor neuropathy), and multifocal motor neuropathy can also mimic HNPP.

When brachial plexopathy is a manifestation of HNPP, neuralgic amyotrophy is the primary alternative consideration and can be acquired (Parsonage-Turner syndrome) or hereditary due to *SEPTIN9* (previously known as *SEPT9*) variations.[53] Clinicians may consider CMT and other hereditary neuropathies when the episodic history is less prominent. Compared with patients with HNPP, patients with CMT1A have more severe distal weakness, atrophy, and slower nerve conduction velocities.

KEY POINTS

- Hereditary neuropathy with liability to pressure palsies typically results from a deletion in *PMP22*, whereas CMT1A typically results from a duplication in *PMP22*.
- Clinicians should consider hereditary neuropathy with liability to pressure palsies in patients with multiple mononeuropathies, especially when painless.
- Distal hereditary motor neuropathies may share common pathophysiologic mechanisms with other motor neuron diseases, such as hereditary spastic paraplegias.

HEREDITARY MOTOR NEUROPATHY

Distal hereditary motor neuropathies are a group of disorders characterized by the almost exclusive involvement of the lower motor neuron without sensory involvement. Some hereditary motor neuropathies are termed *distal spinal muscular atrophy* (SMA), distinguished from classic or proximal SMA by the clinically distal-predominant weakness. The leading theory is that distal hereditary motor neuropathies do not localize to the anterior horn cell but to the motor nerve axon. Nomenclature trends favor a more gene-focused terminology.[54] Responsible genes encode proteins with a wide variety of functions, with gene variants leading to abnormal protein synthesis, mitochondrial dysfunction, impaired chaperone function, altered apoptotic mechanisms, impaired axonal trafficking, impaired ion channel function, and abnormal signaling at the synapse.[55] The inheritance pattern can be autosomal dominant, autosomal recessive, or X-linked.

Clinically, these disorders present with slowly progressive length-dependent weakness and atrophy with reduced or absent reflexes and relatively preserved sensation. While most hereditary motor neuropathies start with lower extremity weakness of the feet and ankles, some have an upper extremity predominance. Onset is typically within the first two decades of life. The hereditary motor neuropathies or neuronopathies that exhibit upper motor neuron involvement overlap clinically with juvenile amyotrophic lateral sclerosis (ALS) and hereditary spastic paraplegias.[55-57]

Respiratory and bulbar symptoms in hereditary motor neuropathies are rare, with a few exceptions. SMA with respiratory distress type 1 due to autosomal recessive variations in *IGHMBP2* presents with respiratory failure from bilateral or unilateral diaphragmatic paralysis in the first year of life.[58] Gene replacement therapy for *IGHMBP2*-related disease is in early clinical trials.[59] Distal hereditary motor neuropathies type VII, caused by autosomal dominant variations in *SLC5A7* (type 7A) or *DCTN1* (type 7B), is characterized by vocal cord paralysis with hand weakness and atrophy initially presenting in childhood or early adulthood.[60,61] Vocal cord paralysis is also described in neuropathy syndromes related to *TRPV4* (type 8), including a scapuloperoneal distal motor neuropathy phenotype.[62,63]

Electrophysiology is particularly helpful in distinguishing hereditary motor neuropathies from other differential diagnoses. Hereditary motor neuropathies will have low-amplitude compound muscle action potentials and preserved sensory responses on nerve conduction studies, with chronic neurogenic findings on needle EMG. Compared with motor neuron disorders such as SMA or ALS, the chronic neurogenic findings in hereditary motor neuropathies are primarily seen in distal muscles. Distal myopathies can clinically mimic hereditary motor neuropathies and can be differentiated by EMG. Some genes associated with hereditary motor neuropathies also have a CMT2 phenotype. Examples include

neuropathies associated with *SORD,*[39] *TRPV4,*[62,63] *GARS1,*[64] *HSPB1,*[65] and *HSPB8.*[65,66]

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY

HSAN is a group of hereditary neuropathies characterized predominantly by the degeneration of sensory and autonomic fibers. Clinically, these disorders present with distal sensory loss and variable degrees of motor weakness and autonomic dysfunction. These patients often have dramatic skin ulcerations that may require acral amputation. Children may exhibit self-injurious behavior because they do not feel the pain associated with injury. Some patients may experience lancinating painful radiculopathies. Autonomic symptoms can include heart rate or blood pressure fluctuations, abnormal sweating, and gastrointestinal disorders, particularly dysmotility. When autonomic dysfunction is absent, the phenotype may be called *hereditary sensory neuropathy*. Congenital insensitivity to pain sometimes refers to HSAN and hereditary sensory neuropathy phenotypes with symptom onset at or near birth. These syndromes generally manifest with an absence of sensory or pain perception. In contrast, primary erythromelalgia, a condition characterized by temperature-sensitive pain and skin erythema, and genetic forms of small fiber neuropathy present with severe chronic neuropathic pain from small fiber dysfunction. While the pathology in these disorders lies in the peripheral sensory nerves, central sensitization to pain may occur.[67]

These sensory-predominant hereditary neuropathies can be inherited in an autosomal dominant or autosomal recessive manner, with the latter typically resulting in an earlier onset in infancy through childhood. Mechanisms underlying this group of disorders are diverse and include defects in the development of sensory neurons, degeneration of sensory neurons, and aberrant signaling and excitability mediated by ion channels.[68]

HSAN1 is the most common HSAN subtype and is associated with five different genes, all with autosomal dominant inheritance. Most commonly, HSAN1 is caused by missense variations in *SPTLC1* (HSAN1A) or *SPTLC2* (HSAN1B), both of which encode a subunit of serine palmitoyltransferase, which is involved in the synthesis of sphingolipids.[68,69] *SPTLC1*-related HSAN1 is the most common and typically begins with painless injuries in adolescence and early adulthood. While sensory loss is the primary symptom, positive sensory phenomena such as paresthesia, burning, stabbing, or shooting pains can develop over time. Skin ulceration, poor wound healing, Charcot joints (neurogenic joint deformity), and limb amputation are common. Additionally, distal motor weakness is relatively common. Autonomic dysfunction can occur but may be less prominent than in other HSAN subtypes. Electrodiagnostic testing can appear normal at early stages, but over time patients will have a reduction first of sensory nerve action potential amplitudes and then of compound muscle action potential amplitudes. Recently, *SPTLC1* variations were identified in patients with juvenile-onset ALS.[70,71] In contrast to HSAN1-associated *SPTLC1* variations that lead to a toxic accumulation of deoxysphingolipids through alterations in the serine palmitoyltransferase substrate, *SPTLC1* variations that cause juvenile-onset ALS result in the hyperactivity of the serine palmitoyltransferase enzyme.[71] Oral L-serine supplementation reduces the production of neurotoxic deoxysphingolipids and may slow disease progression of HSAN1 caused by *SPTLC1* variants.[72]

Voltage-gated sodium channels play an important role in the transmission of pain in sensory fibers. Variations in *SCN9A,* which encodes the $Na_v1.7$ subunit, lead to neuropathies with pain dysregulation. Homozygous loss-of-function variations result in congenital insensitivity to pain and HSAN2 with anosmia. However, heterozygous gain-of-function variations in *SCN9A* and *SCN10A* produce pain syndromes such as paroxysmal extreme pain disorder, primary erythromelalgia, and small fiber neuropathy. *SCN11A,* which encodes the $Na_v1.9$ subunit, also produces a variety of sensory neuropathy phenotypes. Certain heterozygous gain-of-function variations are associated with pain insensitivity and gastrointestinal dysmotility, hypotonia, increased sweating, and extreme itching (congenital insensitivity to pain [HSAN7]), whereas other heterozygous gain-of-function variants lead to small fiber neuropathy and episodic pain syndromes.[73-78]

HSAN2-6 and HSAN8 all have an autosomal recessive inheritance and multiple gene associations: *WNK1* (HSAN2A), *RETREG1* (HSAN2B), *KIF1A* (HSAN2C), *SCN9A* (HSAN2D), *ELP1* (HSAN3), *NTRK1* (HSAN4), *NGF* (HSAN5), *DST* (HSAN6) and *PRDM12* (HSAN8). The *ELP1*-related HSAN3 phenotype, historically called *Riley-Day syndrome*, has the most prominent autonomic dysfunction with small fiber sensory loss and onset at birth and occurs predominantly in those with Ashkenazi Jewish ancestry. HSAN4 and HSAN5 similarly present in childhood with congenital insensitivity to pain and temperature sensation loss.[79] HSAN4 is also uniquely associated with variable degrees of intellectual disability and anhidrosis, which can be complicated by life-threatening hyperthermia.[79] *DST*-related HSAN6 is rare but has a severe presentation early in life with neonatal hypotonia, respiratory failure, areflexia, and dysautonomia.[80]

KEY POINT

- **Hereditary sensory and autonomic neuropathies can manifest with reduced sensation, pain, or both.**

HEREDITARY NEURALGIC AMYOTROPHY

Hereditary neuralgic amyotrophy, also known as hereditary brachial plexus neuropathy or hereditary brachial neuritis, is an autosomal dominant disorder that typically presents with a recurrent painful brachial plexus neuropathy. Individual episodes are clinically and electrophysiologically indistinguishable from the common idiopathic neuralgic amyotrophy or Parsonage-Turner syndrome. However, recurrent episodes, symptoms presenting in a young patient, or a family history of neuralgic amyotrophy should raise clinical suspicion for this hereditary disorder. While most attacks affect the brachial plexus, occasionally the lumbosacral plexus is affected. Variations in *SEPTIN9* have been identified in many patients with hereditary neuralgic amyotrophy, although not in all cases.[53,81] *SEPTIN9* variations have also been associated with a CMT phenotype with cognitive symptoms.[82]

OTHER GENETIC DISORDERS WITH ASSOCIATED NEUROPATHY

Peripheral neuropathy is a component of many complex genetic syndromes that may also have central nervous system involvement and systemic manifestations outside the nervous system.

Hereditary spastic paraplegias are a group of heterogeneous disorders that primarily affect the corticospinal tract, leading to spasticity and gait dysfunction. Uncomplicated or “pure” hereditary spastic paraplegias present with spasticity predominantly of the legs, hyperreflexia, and in some cases weakness, dysfunction, or both, of the bowel and bladder. Complicated

hereditary spastic paraplegias have these features and additional manifestations including cognitive impairment, epilepsy, ataxia, brain malformations, and neuropathy.[83] The peripheral neuropathy can be sensory, motor, or both. Some hereditary spastic paraplegias with neuropathy may represent a continuum with CMT and hereditary motor neuropathies and share disease pathophysiology.

Spinocerebellar ataxia and other hereditary ataxia syndromes are similarly heterogeneous, and manifestations can include peripheral neuropathy. Spinocerebellar ataxias are characterized by slowly progressive cerebellar ataxia, often with accompanying symptoms such as ocular motor dysfunction, dysarthria, intellectual disability, spasticity, dystonia, and peripheral neuropathy. Spinocerebellar ataxia type 4, in particular, is associated with axonal sensory neuropathy.[84]

Friedreich ataxia is typically a pediatric-onset neurodegenerative disorder that presents with gait instability, dysarthria, dysphagia, weakness, sensory loss, lower extremity spasticity, scoliosis, and less commonly optic atrophy and sensorineural hearing loss. Nonneurologic manifestations include cardiac disease and diabetes. Sometimes children with Friedreich ataxia may be thought to have CMT when they present with clumsiness and areflexia and do not yet have the bulbar symptoms and upper motor neuron signs. The peripheral neuropathy is a pure sensory neuropathy or neuronopathy.[85] Degeneration of proprioceptive sensory nerves may significantly contribute to the ataxia. Genetically, Friedreich ataxia is caused by autosomal recessive GAA repeat expansions in the frataxin gene (*FXN*). The pathophysiology of Friedreich ataxia is complex and involves mitochondrial electron transport chain dysfunction, oxidative stress, and possibly dysregulated iron metabolism.[86] The first treatment for Friedreich ataxia, omaveloxolone, was approved in 2023. Omaveloxolone is a small molecule that enhances the nuclear erythroid 2-related factor signaling pathway, which is involved in the synthesis of many antioxidants. Approval of this therapy was based on the Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe) study, which was a randomized double-blind placebo-controlled clinical trial that demonstrated a significant improvement in the modified Friedrich Ataxia Rating Scale in patients aged 16 to 40 years.[87]

Ataxia telangiectasia, caused by autosomal recessive variations in *ATM*, is another pediatric-onset neurodegenerative ataxia syndrome with a peripheral neuropathy component. Compared with Friedreich ataxia, it typically presents with ataxia earlier in childhood; most patients have choreoathetosis, and nonneurologic manifestations include telangiectasias and immunodeficiency. The peripheral neuropathy in ataxia telangiectasia and two other DNA repair disorders (ataxia with oculomotor apraxia types 1 and 2) is a distal-predominant sensorimotor axonal neuropathy.

Giant axonal neuropathy is a rare autosomal recessive neurodegenerative disorder caused by biallelic variations in *GAN* leading to the loss of function of gigaxonin and the subsequent accumulation of intermediate filaments in nerve axons. This accumulation leads to their pathologic "giant" appearance. Clinically, patients develop weakness, gait difficulties, and areflexia in the first few years of life, with variable degrees of spasticity, ataxia, nystagmus, dysarthria, dysphagia, and gastrointestinal dysmotility. Patients with giant axonal neuropathy also have distinctive tightly curled hair that may help distinguish the diagnosis from other peripheral neuropathies and hereditary

ataxia syndromes. Currently, intrathecal delivery of an adeno-associated virus–based gene replacement therapy is in clinical trials.[88]

CANVAS (cerebellar ataxia with neuropathy and vestibular areflexia syndrome) is an adult-onset ataxia syndrome with a predominantly sensory neuropathy or neuronopathy like Friedreich ataxia.[89,90] This is a clinically heterogeneous group of patients with typical features including gait imbalance, coordination difficulties, prominent ocular motor abnormalities, vestibular dysfunction, and length-dependent or non–length-dependent sensory loss. CANVAS is caused by biallelic intronic expansions in *RFC1*.[91] An isolated sensory axonal neuropathy, sometimes associated with a chronic cough or subtle vestibular and cerebellar signs, may signify a milder spectrum of disease associated with biallelic expansions in *RFC1*.[89]

Many hereditary ataxias are due to repeat expansions and may not be routinely detected on next-generation sequencing gene panels or whole-exome sequencing. Therefore, targeted testing may be required if spinocerebellar ataxia, Friedreich ataxia, or CANVAS is on the differential diagnosis.

A range of mitochondrial disorders can lead to energy failure in peripheral nerve axons and produce a variety of peripheral nerve disorders that accompany multisystem manifestations. A few notable mitochondrial syndromes with neuropathy include mitochondrial neurogastrointestinal encephalopathy; sensory ataxia neuropathy, dysarthria, and ophthalmoparesis; and mitochondrial cerebellar ataxia, renal failure, neuropathy, and encephalopathy.

Lysosomal storage disorders are a diverse group of diseases that share the common pathophysiology of the aggregation of toxic material in lysosomes. Fabry disease, Krabbe disease, and metachromatic leukodystrophy all have a peripheral neuropathy component. Fabry disease, an X-linked recessive condition caused by variations in the α-galactosidase A gene, distinctively produces a small fiber neuropathy that presents in young boys with episodic burning pain similar to the *SCN9A/SCN10A*-related conditions described above.[92] However, Fabry disease also has multisystem clinical features, including typical dermatologic and soft tissue findings (angiokeratomas, acroparesthesia, and lymphedema), gastrointestinal symptoms, vascular disease, and corneal opacities. Fabry disease is important to consider since there are two disease-modifying treatments available, one enzyme replacement therapy and one chaperone therapy. Clinicians can test for Fabry disease via enzymatic testing or genetic testing.

Hereditary amyloidosis is an adult-onset multisystem genetic disorder caused by autosomal recessive *TTR* variations that lead to the accumulation of the amyloid precursor protein, transthyretin. Hereditary amyloidosis must be distinguished from acquired causes of amyloidosis such as immunoglobulin light chain disorders, which also have neuropathic accompaniments. Multiple neuropathy phenotypes can be associated with hereditary amyloidosis, including generalized length-dependent sensorimotor neuropathy, focal neuropathy, and autonomic neuropathy. There are multiple disease-modifying therapies for transthyretin-associated amyloidosis. Tafamidis meglumine is an oral treatment that reduces the misfolding of the altered transthyretin protein. Gene silencing medications include patisiran, vutrisiran, and inotersen. Patisiran and vutrisiran are small interfering RNAs that target the RNA synthesis of TTR to reduce transcription and aggregation of the protein. Inotersen is an antisense oligonucleotide that reduces the production of TTR. All three therapies have been shown to slow progression of neuropathy and improve quality of life. Additional gene therapy approaches are an active area of clinical research.

KEY POINTS

- **Peripheral neuropathy can be a component of a broader syndrome involving the central nervous system, other body systems, or both. Examples include Friedreich ataxia, giant axonal neuropathy, and mitochondrial and metabolic disorders.**

- **Novel therapies for hereditary neuropathies as a whole and for different gene subtypes specifically are an active area of clinical trial interest.**

MANAGEMENT

The mainstay of treatment for CMT and other hereditary neuropathies is symptomatic management with an emphasis on improving gait and function via physical therapy, bracing, and surgical intervention. The specific goals of physical therapy change over time and depend on the severity of weakness and sensory loss and the functional goals of the patient. Physical therapy can help maintain muscle strength in weak muscles and optimize strength in less affected core muscles. Water-based therapies are optimal for patients with neuromuscular disease. When sensory input is affected, causing gait imbalance, physical therapy provides gait and balance training and helps patients use other inputs for spatial awareness. Physical therapists can also help patients understand their functional limits and create a plan to optimize safety. Another crucial role of physical therapy is to develop a stretching regimen to prevent joint contractures, which can become functionally limiting and painful over time. Sometimes serial casting or night splints may be beneficial for heel cord contractures, especially in younger patients. When appropriate, assistive devices for walking, such as braces, canes, walkers, and wheelchairs, may be necessary, and physical therapists can teach patients how to use this equipment. Most people with CMT use ground reaction ankle-foot orthoses to support their distal lower extremity weakness and provide proprioceptive input for their lower legs.

Many patients with hereditary neuropathy have a resulting foot deformity, typically a cavovarus deformity. This foot morphology alters the weight-bearing distribution in the foot and can lead to callous formation, irritation caused by footwear, and pain. Early management includes stretching and bracing to slow the progression of the deformity, but some patients may require surgery when bracing and physical therapy do not address the pain and limitations. The goal of any surgical strategy should be to stabilize the foot, improve function, and reduce pain.[16] There are multiple surgical approaches ranging from soft tissue release, tendon transfer, osteotomy, and full reconstruction.[93] Joint fixation (eg, arthrodesis) is often the last resort. It is important to recognize that hereditary neuropathies are progressive, and there is a risk of recurrence despite surgery.[93] The clinician should have a thorough discussion with the patient and their family to determine the right time and best surgical approach.

FUTURE DIRECTIONS

There is ongoing research exploring different treatment mechanisms for hereditary neuropathies. Multiple gene therapy approaches, including gene silencing (CMT1A), allele-specific silencing (CMT2E), gene replacement (CMTX1, CMT4A, CMT4C, CMT2A), gene editing with CRISPR-Cas9 (CMT1A, CMT2A, CMT2D-F), and antisense oligonucleotides (CMT1A) are under development. Some approaches, such as small molecules, enzyme replacements, and antioxidants, target common downstream pathways in hereditary neuropathies.[94-97]

CONCLUSION

Hereditary neuropathies encompass a spectrum of motor and sensory neuropathies with axonal or demyelinating features caused by genetic defects that affect various nerve functions. Hereditary neuropathies continue to be classified by phenotype; therefore, thorough clinical evaluation and electrophysiology are

essential in diagnosing patients. However, a gene-based perspective is emerging, particularly since many of the therapeutic approaches in development are gene targeted. While newer disease-modifying treatments are on the horizon, physical therapy and orthopedic management remain the mainstay of treatment.

VIDEO LEGENDS

VIDEO 10-1
Video shows a 30-year-old man with Charcot-Marie-Tooth disease type X1 with gait abnormality in the form of steppage and ataxia.

VIDEO 10-2
Video shows a 60-year-old woman with Charcot-Marie-Tooth disease type 1A and gait abnormality with and without ground reaction ankle-foot orthotics.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

By Aaron Izenberg, MD

ABSTRACT

OBJECTIVE: **This article reviews the clinical spectrum of amyotrophic lateral sclerosis (ALS), its variant presentations, and the approach to diagnosis and management. This review includes a detailed discussion of current and emerging disease-modifying therapies and the management of respiratory and bulbar manifestations of disease. An updated review of ALS genetics and pathophysiology is also provided. This article also touches on several other important motor neuron diseases.**

LATEST DEVELOPMENTS: **A new set of simplified diagnostic criteria may help identify patients at earlier stages of the disease. A coformulation of sodium phenylbutyrate and tauroursodeoxycholic acid has been shown to have a significant benefit on disease progression and survival, leading to approval by regulatory authorities in the United States and Canada. An oral formulation of edaravone and an antisense oligonucleotide to a *SOD1* gene variation (tofersen) have also recently been approved by the US Food and Drug Administration (FDA). Phase 3 trials of intrathecal mesenchymal stem cells failed to meet primary end points for efficacy. Updated American Academy of Neurology quality measures for the care of patients with ALS were published in 2023.**

ESSENTIAL POINTS: **There has been continued progress in ALS genetics, diagnosis, and disease-modifying therapies. However, we still lack a definitive biomarker or a treatment that can halt the progression or reverse the course of disease. The evolving understanding of the genetic and pathophysiologic underpinnings of disease offers promise for more effective and clinically meaningful treatments in the future.**

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Address correspondence to Dr Aaron Izenberg, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto, Ontario, M4N 3M5, Canada, aaron.izenberg@sunnybrook.ca.

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INTRODUCTION

The term *motor neuron disease* refers to a group of conditions that are characterized by injury to lower motor neurons (LMNs), upper motor neurons (UMNs), or both. Although this review focuses on amyotrophic lateral sclerosis (ALS), it is essential to recognize that other acquired and hereditary motor neuron diseases may present with similar features (TABLE 11-1).

These conditions primarily affect the cell body of the motor neuron and are thus considered neuronopathies rather than neuropathies. The UMN cell bodies

reside in the primary motor cortex, and their axons descend through the brain via the corticobulbar pathways and corticospinal pathways. The latter decussate in the medulla and continue in the lateral corticospinal tracts of the spinal cord. The corticobulbar pathways synapse on cranial nerve motor nuclei, and corticospinal pathways synapse on LMN cell bodies in the anterior horn of the spinal cord. Axons of cranial nerve motor nuclei and anterior horn cells ultimately synapse with bulbar, respiratory, truncal, and limb muscles. Injury to these pathways can result in bulbar, axial, limb, and respiratory weakness.

EPIDEMIOLOGY

The global incidence of ALS is approximately 2 per 100,000 people/year, whereas the prevalence is 5 per 100,000 people.[1-4] Men are more commonly affected, with an incidence ratio of approximately 1.5 compared with women. ALS most commonly presents between the ages of 60 and 75 years, although the disease can present from the second to beyond the ninth decade of life.[1]

Age, family history, and cigarette smoking are well-established risk factors for developing ALS.[5] Other potential environmental risk factors have been reported, although some with weaker levels of evidence. Higher levels of physical activity and participation in sports associated with concussion have been reported to increase the risk of disease.[6,7] Exposure to heavy metals, electromagnetic fields, and toxins such as pesticides have also been cited as possible risk factors.[8] Military service also carries an increased risk of disease, regardless of branch or the timing of service.[9]

CLINICAL FEATURES

The characteristic motor symptoms of ALS can ultimately all be attributed to the loss of UMNs and LMNs in the brain, brainstem, and spinal cord. However, the presentation of the disease is heterogeneous, depending on where in the neuraxis the degeneration begins.

Patients most commonly present with asymmetric lower limb weakness (ie, lumbosacral segment), asymmetric upper limb weakness (ie, cervical segment),

The Spectrum of Motor Neuron Diseases TABLE 11-1

	Upper motor neuron	Upper and lower motor neuron	Lower motor neuron
Acquired	Primary lateral sclerosis	Amyotrophic lateral sclerosis (ALS)	Progressive muscular atrophy Monomelic amyotrophy Facial-onset sensory and motor neuronopathy Infectious: poliomyelitis and West Nile virus
Hereditary	Hereditary spastic paraparesis	Familial ALS Spinocerebellar ataxia 3	Spinal muscular atrophy Kennedy disease Fazio-Londe syndrome, Brown-Vialetto-van Laere syndrome

or bulbar manifestations. Each of these phenotypes accounts for approximately 25% to 30% of patients at presentation.[10]

Less common presentations include respiratory weakness and head drop. There are also several distinct clinical variants, including patients with predominant UMN involvement (primary lateral sclerosis [PLS]), LMN involvement (progressive muscular atrophy), flail arm and flail leg presentations, pseudobulbar palsy, and hemiplegic ALS (eg, Mills syndrome). Rates of progression vary widely.

The clinician must, therefore, be familiar with the phenotypic spectrum of ALS and related variants. There is still no gold standard diagnostic test or biomarker, and clinical recognition remains the cornerstone of diagnosis.

Limb Manifestations

Limb weakness typically begins in distal muscles. Patients with upper limb onset may initially report hand clumsiness or difficulty performing common tasks, such as closing buttons or opening jars. In lower limb onset, foot drop is a common initial manifestation, and patients may report frequent tripping or "foot slapping." These patients may be referred for evaluation of more common conditions such as carpal tunnel syndrome or lumbosacral radiculopathy. However, the lack of pain or sensory symptoms accompanying progressive weakness will alert the clinician to a more ominous diagnosis.

With time, progression into more proximal limb muscles is expected. Involvement of the upper arm and shoulder will interfere with overhead tasks such as dressing and hair washing, and weakness of hip and thigh muscles will manifest with difficulty going up stairs and standing from a seated position.

LMN involvement typically results in muscle cramps, which can be quite painful and disruptive to sleep. Fasciculations are also usually present. The patient should be examined while wearing a gown with both arms and legs, shoulders, and upper chest exposed. With proper exposure, observation with indirect lighting for even 30 to 60 seconds will often reveal profuse fasciculations that the patient may not have noticed. It is important to note that ALS rarely presents with isolated fasciculations in the absence of weakness or other upper or LMN findings. In this scenario, fasciculations are usually benign or attributable to another neurogenic process.

UMN involvement often results in limb spasticity, which may be experienced as stiffness or slowness of movement by patients. Spasticity in the lower limbs will typically cause difficulty with balance and may lead to falls. Hyperreflexia is also evident on examination. However, in this author's experience, plantar responses are often flexor or mute, whereas the Hoffmann sign or Trömner sign is frequently present. Patients with a UMN-dominant presentation often have less marked weakness on examination.

Bulbar Manifestations

Bulbar manifestations can yield the most characteristic and distinctive presentations of ALS. For example, in an adult with a new onset of progressive mixed spastic-flaccid dysarthria, tongue atrophy and fasciculations, and no underlying abnormalities on imaging, the diagnosis can be made almost immediately. Bulbar involvement is characterized by dysarthria and dysphagia, and typically patients present with features of both.

UMN degeneration results in spastic dysarthria, which is slow, strained, and often louder. Lingual movements are slow and labored, and the patient may be unable to protrude the tongue. LMN involvement causes weakness of the lips, tongue, and palate, resulting in a flaccid dysarthria that is hypernasal, quieter, and at times breathy. Proper assessment for fasciculations requires that the tongue be completely at rest, which is often challenging for patients. Caution should be taken in characterizing movements as fasciculations in the absence of tongue atrophy considering the tongue's frequent movements. Atrophy is also often seen and results in a corrugated or "raisinlike" appearance of the tongue. Laryngeal involvement may result in a component of dysphonia or hoarseness. Laryngospasm is caused by UMN involvement and results in brief episodes of stridor and difficulty with inspiration.

Pseudobulbar affect is a UMN feature of ALS, characterized by uncontrollable and, at times, intrusive bouts of laughing or crying. These episodes are incongruent or excessive with respect to the actual emotional state and can be disruptive and upsetting to patients and their caregivers. Up to 30% of patients with ALS may develop pseudobulbar affect.[11]

Respiratory Manifestations

Weakness of the diaphragm and other respiratory muscles results in worsening dyspnea with exertion and at rest. Orthopnea is a characteristic manifestation, and diaphragmatic weakness may be exposed when transitioning from an upright to a supine position. Patients may also endorse features of sleep-disordered breathing, including excessive daytime sleepiness and morning headaches. Expiratory muscle involvement often leads to a weak cough and difficulty with secretion clearance. On examination, there may be accessory muscle use, paradoxical breathing, and shortness of breath with speaking.

Cognitive Manifestations

Although the features discussed in the previous paragraphs often dominate the clinical picture, nonmotor manifestations of ALS can also cause significant morbidity. Approximately 50% of patients with ALS will have some degree of cognitive or behavioral dysfunction on neuropsychological assessment, and about 15% of patients will develop frontotemporal dementia (FTD).[12–14] A similar proportion of patients initially diagnosed with FTD will develop features of ALS. It is not uncommon for patients with FTD to be referred by their cognitive specialists for concern of evolving weakness or other motor features (**CASE 11-1**).

Patients with ALS-FTD most commonly manifest behavioral features, including disinhibition, apathy, and loss of empathy. This is a particularly cruel feature of the disease, because it can cause significant disruption in patients' personal relationships and may alienate loved ones. Identifying these behaviors as manifestations of the neurologic disease can be important for family dynamics and may inform decisions surrounding patients' care and living arrangements.

Importantly, the co-occurrence of ALS and FTD portends a higher risk of an underlying genetic variation. For example, patients with *C9orf72* variations have a significantly higher risk of cognitive impairment (40% to 50%) compared with those without.[15,16]

KEY POINTS

- **Amyotrophic lateral sclerosis (ALS) has a heterogeneous clinical phenotype. The three most common presentations are that of lower limb, upper limb, and bulbar weakness, with each accounting for 25% to 30% of patients.**
- **Distal limb muscles are typically affected first in patients with ALS, with subsequent progression to proximal muscles. Upper motor neuron involvement results in more stiffness and slowness of movement and usually causes less weakness than lower motor neuron loss.**
- **Up to 30% of patients with ALS may develop pseudobulbar affect.**
- **Orthopnea and symptoms of sleep-disordered breathing are characteristic features of respiratory involvement in ALS.**

VARIANT PRESENTATIONS

Although ALS most commonly presents with characteristic UMN and LMN findings spanning multiple body regions, there are also several well-described variant presentations. These syndromes often do not satisfy formal diagnostic criteria (discussed later in this article) because of preferential UMN or LMN involvement or restriction to one body region. However, these are still acquired degenerative motor neuron diseases. Each syndrome typically involves a distinct clinical course, prognosis, and differential diagnosis, but many specialists would consider these variants to exist in a spectrum of disease that includes ALS.[17] Indeed, some will evolve into more characteristic cases of ALS that satisfy the diagnostic criteria of that disorder.

Primary Lateral Sclerosis

PLS is a disorder characterized by isolated UMN degeneration. Patients typically present with gradually progressive leg followed by arm spasticity and stiffness and spastic dysarthria. PLS commonly presents with bilateral lower limb stiffness and falls, and patients may report imbalance rather than weakness. It is essential to recognize that a significant proportion of patients presenting with isolated UMN findings will subsequently develop LMN manifestations, in keeping with an ALS phenotype.[18] Recent consensus diagnostic criteria suggest a classification

CASE 11-1

A 52-year-old man with a 4-month history of right upper limb weakness was referred for electrodiagnostic evaluation. He first noticed difficulty using his right hand to use tools and subsequently developed more obvious weakness and atrophy in his right forearm and biceps. The patient's wife also reported that his speech seemed to be more slurred and that he was "talking less and less." He did not endorse any dysphagia, respiratory symptoms, weakness in his other limbs, behavioral changes, or memory difficulty. His examination revealed atrophy and grade 4-/5 to 4+/5 weakness in his right upper limb (worse distally) and atrophy and fasciculations in all four limbs. He had a mild spastic dysarthria. On assessment of language, he had decreased verbal fluency and difficulty with naming and repetition with preserved comprehension. The remainder of the neurologic examination was unremarkable. Needle EMG revealed active and chronic denervation in his right upper limb muscles and his tongue with sparing of thoracic and lumbosacral segments, although fasciculation potentials were widespread.

Over the following year, he had progressive difficulty with speech output, and he eventually became mute. He also developed weakness in his left hand and right ankle.

COMMENT

This patient presented with concurrent upper limb weakness and features of primary progressive aphasia (nonfluent variant), and he was diagnosed with amyotrophic lateral sclerosis with frontotemporal dementia. Genetic testing for *C9orf72*, *ATXN2*, and a sequencing panel of other disease-associated genes was negative.

of probable PLS for patients with isolated UMN involvement between 2 and 4 years from symptom onset and definite PLS beyond 4 years.[19] However, it should be recognized that a smaller percentage of patients will develop LMN features later in the course of the disease, even up to 10 years after symptom onset.[20] Regardless of whether the course remains compatible with PLS or evolves into a UMN-predominant form of ALS, these patients have a more favorable prognosis with a longer course of disease.[21]

Patients with PLS can have an appearance similar to hereditary spastic paraparesis (HSP), a familial condition that also typically presents with bilateral lower limb spasticity and weakness. However, HSP often presents with bladder dysfunction and sensory manifestations and usually with spared upper limb and bulbar muscles. In addition, patients with HSP may have a familial pattern and tend to have a more gradual progression than those with PLS.

Progressive Muscular Atrophy

Progressive muscular atrophy represents the other end of the neuroanatomic spectrum of acquired motor neuron disease. It is characterized by isolated LMN involvement with no apparent UMN symptoms or signs on examination. In approximately 20% of patients, UMN features will ultimately develop,[22] and autopsy studies have demonstrated evidence of UMN pathology in patients with a progressive muscular atrophy phenotype.[23] Similar to PLS, progressive muscular atrophy is typically associated with more prolonged survival.

Flail Arm and Flail Leg Variants

Flail arm syndrome (also known as *brachial amyotrophic diplegia*) is characterized by bilateral, asymmetric, LMN weakness and atrophy affecting both upper limbs with sparing of other body regions. Weakness commonly begins proximally with subsequent spread to distal muscles. Flail leg syndrome similarly presents with bilateral, symmetric LMN weakness in the legs, although more commonly with onset in distal muscles (CASE 11-2).

EMG should reveal denervation isolated to cervical segments in the flail arm variant and lumbosacral segments in the flail leg variant.[23] However, a milder degree of denervation may be seen in segments outside the clinically affected limbs in patients who otherwise conform phenotypically to one of these variants. Both flail limb variants carry a more favorable prognosis, with a significant percentage of patients surviving beyond 5 years.[24]

Progressive Bulbar Palsy

Progressive bulbar palsy is an isolated bulbar-onset syndrome that can be associated with involvement of either LMNs or UMNs or both. Although the clinical phenotype is characterized by prominent dysphagia and dysarthria, some patients will also have evidence of limb denervation on initial EMG; for a majority of these patients, it will evolve into a more characteristic ALS phenotype.[25] The degree of dysphagia at presentation often necessitates early and expeditious consideration of gastronomy tube insertion.

DIAGNOSIS

In the absence of a gold-standard test or biomarker, ALS continues to be primarily a clinical diagnosis. The clinician must recognize features suggestive of ALS while simultaneously excluding other potential conditions, particularly

KEY POINTS

- **An isolated upper motor neuron presentation often evolves into a conventional ALS phenotype.**
- **Recent consensus diagnostic criteria suggest a classification of probable primary lateral sclerosis for patients with isolated upper motor neuron involvement between 2 and 4 years from symptom onset and definite primary lateral sclerosis beyond 4 years.**
- **Progressive muscular atrophy and primary lateral sclerosis both have a more favorable prognosis than ALS.**

CASE 11-2

A 77-year-old man presented to clinic with a 2-year history of bilateral leg weakness. He started noticing weakness in his right ankle, causing him to trip when walking. Over the following year, he developed progressive weakness and atrophy in his right calf and thigh, followed by the same in his left leg. He had no sensory symptoms, pain, upper limb weakness, dysphagia, dysarthria, or respiratory symptoms. His examination revealed atrophy and fasciculations in his thighs and calves (FIGURE 11-1) with grade 1/5 to 2/5 weakness in all lower limb muscles bilaterally. Muscle stretch reflexes were normal in his upper limbs and unobtainable in his lower limbs. The remainder of the neurologic examination was unremarkable. Needle EMG revealed active and chronic denervation in all leg muscles tested, with sparing of thoracic paraspinal and arm muscles. Nerve conduction studies revealed low-amplitude compound muscle action potentials in the lower limbs and were otherwise normal, and an MRI of the whole spine revealed only mild degenerative changes. Weakness and atrophy remained confined to the lower limbs for the next 4 years, and annual repeat EMG testing was unchanged. Approximately 5 years after his initial presentation, he developed weakness and atrophy in his right hand, followed 1 year later by the same in his left hand. Repeat EMG revealed interval development of active and chronic denervation in cervical and thoracic segments.

FIGURE 11-1
Photograph of the patient in CASE 11-2 with the flail leg variant of amyotrophic lateral sclerosis. Marked, distal-predominant atrophy can be seen in both lower limbs.

COMMENT

This patient was diagnosed with the flail leg variant of amyotrophic lateral sclerosis (ALS). He presented with bilateral lower limb weakness and atrophy, with associated denervation only in lumbosacral segments. His disease remained restricted to lumbosacral segments for approximately 5 years, at which point he developed weakness in his hands, with accompanying cervical and thoracic denervation on EMG. This evolution suggested a generalization of his motor neuron disease. This case illustrates the relatively restricted clinical manifestations and more protracted course that are often seen in the flail leg and flail arm variants of ALS.

those that might be amenable to treatment. The differential diagnosis for ALS largely depends on the clinical phenotype at presentation (TABLE 11-2). Through this process, the clinician should also be mindful of any emerging respiratory or bulbar symptoms that may require intervention, timelines for treatment and clinical trial eligibility, and the psychological stress that patients and families endure while in diagnostic limbo. The workup must be practical and tailored to each patient to ensure a secure and timely diagnosis.

Electrophysiologic testing should be performed in patients with suspected motor neuron disease. Nerve conduction studies may reveal low-amplitude or absent motor responses, and sensory responses should be preserved. Needle EMG typically reveals a combination of active denervation (fibrillation potentials) and chronic denervation in multiple myotomes, often spanning multiple body regions (ie, bulbar, cervical, thoracic, and lumbosacral).[26] Fasciculation potentials may be widespread and profuse, extending beyond the distribution of active denervation.

Several caveats are important to consider concerning electrophysiologic testing in ALS. Incidental electrophysiologic findings, such as carpal tunnel syndrome or peripheral neuropathy, are common. The clinician must account for these concomitant issues when interpreting the study to avoid missing an otherwise compatible electrophysiologic profile. In these cases, the presence of sensory abnormalities should not detract from a suspicion for ALS. It is also essential to recognize that the electrophysiologic manifestations of ALS often evolve with time, and repeat testing may be indicated. Patients with a UMN-dominant presentation may initially have a normal study. For example, in a patient with progressive spastic dysarthria with no other explanation identified on imaging, a normal EMG would not exclude the possibility of ALS.

Imaging of the neuraxis is indicated in virtually all patients and should be guided by the clinical presentation. Brain MRI is typically most useful to exclude other diagnoses and is often unremarkable in ALS. However, T2 hyperintensity can be seen in the descending corticospinal tracts in some patients,[27] and susceptibility-weighted imaging (SWI) can reveal hypointensity in the precentral gyrus (the so-called *motor band sign*) in nearly 80% of patients.[28]

Beyond electrophysiologic testing and imaging, the role of additional investigations is often limited. Laboratory workup usually will not change management and, even more rarely, will result in a change to the primary diagnosis of ALS.[29] However, there can be a role for additional, targeted testing depending on the clinical phenotype. In patients with an LMN-dominant presentation, the addition of serum creatine kinase, West Nile virus, and Lyme disease serology may be indicated. Anti-GM1 antibodies may be sent as a screen for multifocal motor neuropathy (MMN), although increased titers may be seen in more than 15% of patients with ALS.[30] If there are associated ocular features (eg, diplopia, ptosis) or significant fatiguability, additional testing for myasthenia gravis should be pursued, including acetylcholine receptor and muscle-specific kinase (MuSK) antibodies, and repetitive nerve stimulation. Kennedy syndrome should also be considered in men with gynecomastia, increased serum creatine kinase, and other suggestive clinical features (discussed later). However, it is important to recognize that many patients with ALS will have a mild to moderate increase of serum creatine kinase (often less than 1000 U/L).

In cases with a UMN phenotype, additional workup for so-called *imaging-negative myelopathy* should be considered. This may include metabolic and

KEY POINT

- There is no gold-standard diagnostic test or biomarker for ALS. Although all patients should undergo electrophysiologic testing, imaging and bloodwork should be guided by the clinical phenotype.

nutritional disorders (vitamin B_{12}, vitamin E, and copper levels), infections (human immunodeficiency virus [HIV], human T-cell lymphotropic virus types I and II [HTLV-I and -II], syphilis, and Lyme disease serologies), and autoimmune disease (antinuclear antibodies and extractable nuclear antibody panel). In patients with a more chronic course and preferential lower limb involvement, genetic testing for HSP should be pursued.

Genetic testing has an expanding role in ALS, which is discussed in detail later.

TABLE 11-2 **Amyotrophic Lateral Sclerosis Differential Diagnosis Based on Clinical Phenotype**

Condition	Distinguishing features[a]
Upper motor neuron predominant	
Hereditary spastic paraparesis	Sensory symptoms, bowel and bladder dysfunction, leg predominant, possible family history; abnormal genetic testing
Nutritional deficiency: vitamin B_{12}, copper, and vitamin E	Sensory symptoms, peripheral neuropathy, abnormalities on cord imaging
Adrenomyeloneuropathy	Sensory symptoms, peripheral neuropathy, X-linked pattern; abnormal genetic testing (*ABCD1* variation) and very long chain fatty acids
Infection: syphilis, human immunodeficiency virus (HIV) myelopathy, human T-cell lymphotropic virus type I (HTLV-I) infection	History suggestive of infectious illness, sensory symptoms; abnormal serology or CSF
Primary progressive multiple sclerosis	Sensory symptoms, abnormal spine and brain MRI
Lower motor neuron predominant	
Multifocal motor neuropathy	Weakness in peripheral nerve distribution, stepwise progression, improvement or stabilization with intravenous immunoglobulin (IVIg), sparing of bulbar and respiratory muscles; conduction block on nerve conduction studies, elevated anti-GM1 antibodies[b]
Spinal muscular atrophy	Early onset, very chronic course; abnormal genetic testing (homozygous *SMN1* deletion)
Postpolio syndrome	Prior history of polio, limb-length discrepancy, foot deformities, associated fatigue, and pain
Kennedy disease	Gynecomastia, perioral fasciculations, serum creatine kinase >1000 U/L, sensory involvement; abnormal genetic testing (CAG expansion on chromosome X)
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Sensory involvement, demyelinating findings on nerve conduction studies, CSF cytoalbuminologic dissociation
Inclusion body myositis (IBM)	Preferential finger flexor and quadriceps weakness, myopathic findings on EMG
Spondylotic or compressive polyradiculopathy	Radicular pain, sensory symptoms, degenerative findings on spine MRI

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Diagnostic Criteria

The El Escorial criteria for the diagnosis of ALS, most recently revised in 2000, identify five categories of descending certainty of diagnosis and have been used for inclusion into clinical trials.[31] The subsequent Awaji criteria developed in 2008 allowed fasciculations as a clinical and electrophysiologic sign of LMN involvement, with the goal of increasing overall diagnostic sensitivity.[32] Both sets of criteria have been viewed by some as overly complex for clinicians and

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Condition	Distinguishing features[a]
Combined upper and lower motor neuron	
Spondylotic or compressive myelopathy with polyradiculopathy	Radicular pain, sensory symptoms, bowel or bladder dysfunction, degenerative findings on spine MRI
Spinal dural arteriovenous fistula	Abnormal flow voids on spine MRI, cord edema and hyperintensity secondary to venous congestion, evidence of arteriovenous shunting on conventional angiogram
Bulbar onset	
Myasthenia gravis	Associated ocular manifestations, fatiguability, response to immune-based therapies; elevated acetylcholine receptor antibodies or muscle-specific kinase (MuSK) antibodies
Myopathy (eg, oculopharyngeal muscular dystrophy, IBM)	Chronic course, myopathic findings on EMG; abnormal muscle biopsy
Cerebellar disease (eg, multiple system atrophy)	Scanning dysarthria, ataxic and extrapyramidal findings on examination
Infiltrative or compressive lesion in the tongue (eg, squamous cell carcinoma)	Asymmetric or unilateral tongue atrophy and fasciculations; MRI of nasopharynx or neck may be required to reveal a lesion
Head drop	
Myasthenia gravis	Associated ocular manifestations, fatiguability, response to immune-based therapies; elevated acetylcholine receptor antibodies or MuSK antibodies
Myopathy: IBM, congenital myopathy (eg, nemaline)	Chronic course, myopathic findings on EMG; abnormal biopsy of neck extensor muscles
Multiple system atrophy	Head drop due to mechanical restriction or rigidity rather than neck extensor weakness, other features of parkinsonism on examination

CSF = cerebrospinal fluid; EMG = electromyography; MRI = magnetic resonance imaging.
[a] Distinguishing features may not all be present.
[b] Elevated anti-GM1 antibodies may be absent in multifocal motor neuropathy and can rarely be seen in amyotrophic lateral sclerosis.

patients and potentially overinclusive of patients with isolated UMN involvement (ie, PLS).

The recent Gold Coast criteria are more simplified and eliminate definite, probable, and possible classifications (TABLE 11-3).[33] A comparison study revealed that the Gold Coast criteria had sensitivity and specificity similar to the El Escorial criteria and Awaji criteria for diagnosis of all ALS categories.[34] In addition, the Gold Coast criteria had increased overall sensitivity compared with the revised El Escorial criteria and Awaji criteria for definite and probable ALS, suggesting benefit for detecting patients at earlier stages of the disease. The Gold Coast criteria may therefore be particularly advantageous for earlier initiation of disease-modifying treatments, initiation of multidisciplinary care, and enrollment into clinical trials.

GENETICS

Approximately 90% of patients with ALS have no known family history and are thus classified as having sporadic disease. Familial ALS related to mendelian, monogenic inheritance occurs in at least 10% of patients with ALS, and most of these cases are inherited in an autosomal dominant manner.[35] However, family

TABLE 11-3

The Gold Coast Diagnostic Criteria for Amyotrophic Lateral Sclerosis[a]

Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function

AND

Presence of upper[b] and lower[c] motor neuron dysfunction in at least one body region[d] (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) OR lower motor neuron dysfunction in at least two body regions

AND

Investigations[e] excluding other disease processes

[a] Modified with permission from Shefner JM, et al, Clin Neurophysiol.[33] © 2020 Elsevier Ltd.

[b] Upper motor neuron dysfunction implies at least one of the following:

(1) Increased muscle stretch reflexes, including the presence of a reflex in a clinically weak and wasted muscle, or spread to adjacent muscles

(2) Presence of pathologic reflexes, including the Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex

(3) Increase in velocity-dependent tone (spasticity)

(4) Slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or parkinsonian features

[c] Lower motor neuron dysfunction in a given muscle requires either:

Clinical examination evidence of muscle weakness and wasting

OR

EMG abnormalities that must include:

Evidence of chronic neurogenic change, defined by large motor unit potentials of increased duration or increased amplitude or both, with polyphasia and motor unit instability regarded as supportive but not obligatory evidence

AND

Evidence of ongoing denervation including fibrillation potentials, positive sharp waves, or fasciculation potentials

[d] Body regions are defined as bulbar, cervical, thoracic, and lumbosacral. To be classified as an involved region with respect to lower motor neuron involvement, there must be abnormalities in two limb muscles innervated by different roots and nerves, or one bulbar muscle, or one thoracic muscle either by clinical examination or by EMG.

[e] The appropriate investigations depend on the clinical presentation and may include nerve conduction studies and needle EMG, MRI or other imaging, fluid studies of blood or CSF, or other modalities as clinically necessary.

history can be limited by myriad factors such as premature parental death and adoption, and a small percentage of patients with sporadic disease may have a genetic cause of disease. It is well recognized that the majority of known pathogenic variations have been identified in patients with sporadic diseases, and *C9orf72* expansions have been seen in 3% of this population.[36,37] In fact, pathogenic variations may be found in up to 15% of patients with sporadic disease, particularly as additional genes are discovered and testing becomes more frequent.[38]

It is essential to recognize that the role of genetic makeup is more complex than a simple dichotomy into familial and sporadic disease. Oligogenic and polygenic models of pathophysiology have identified multiple genetic variants that can increase the risk of disease.[39] It is also important to recognize that there is a complex combination of genetic and environmental factors that determine the risk of developing ALS. Heritability, the degree to which the risk of developing disease is attributable to genetic factors, has been estimated at greater than 50% in some populations of patients with sporadic ALS.[40]

The list of monogenic variations that have been implicated in the development of this disease is growing. The *SOD1* variation was described in 1993 and is still the second most common cause of familial ALS.[35] Variations are 90% penetrant by the age of 70, and more than 200 variants have been identified.[41] Pathogenic variants are thought to mediate disease through multiple pathways, including oxidative stress and inflammation.[10]

The next significant development in ALS genetics came in 2001 when a pathogenic variation of the Alsin gene on chromosome 2 (*ALS2*) was identified as a cause of autosomal recessive familial ALS occurring in children.[42] The next decade saw the discovery of multiple additional causative genes, including *TARDBP*, which encodes the transactive response DNA-binding protein (TDP-43), in 2008. This discovery provided an important link between a pathogenic variation and the hallmark pathologic finding of cytoplasmic TDP-43 aggregation in motor neurons that is seen in more than 90% of patients with sporadic ALS.

In 2011, a hexanucleotide repeat expansion in the *C9orf72* gene on chromosome 9 was identified as a cause of autosomal dominant familial ALS.[43,44] Pathogenic variations are thought to cause disease through toxic gain and loss of function. The *C9orf72* expansion is the most common monogenic cause of disease, accounting for 40% of familial ALS with a penetrance of up to 100% by age 80. Patients can present with ALS, FTD, or a combination of both. More rarely, *C9orf72* expansions can be associated with features of other neurodegenerative diseases, including parkinsonism, tremor, myoclonus, corticobasal syndrome, Huntington disease–like syndrome, Creutzfeldt-Jakob disease, and Alzheimer disease.[45,46]

In the decade since the discovery of the *C9orf72* expansion, multiple additional causative genes have been described, advancing our understanding of disease pathogenesis and ushering in an era of gene-based therapy development.

Genetic testing has become increasingly accessible as commercial laboratories now offer extensive panels covering common and rare genes, with some laboratories offering free or sponsored testing. Although any patient may ultimately choose to pursue genetic testing, clinicians must carefully consider when to recommend this.[16] Generally speaking, symptomatic patients with a family history of ALS or FTD should be routinely offered testing.

KEY POINTS

- **The Gold Coast diagnostic criteria for ALS are simpler than the revised El Escorial and Awaji criteria and may be of benefit for diagnosing patients earlier in the disease.**
- **Familial ALS occurs in at least 10% of patients. However, pathogenic gene variations may be found in up to 15% of patients diagnosed with sporadic ALS.**
- **Variations in the *C9orf72* and *SOD1* genes remain the most common genetic causes of familial ALS. However, the list of recognized variations is growing.**

In addition, asymptomatic relatives of patients with suspected or confirmed ALS may seek testing and genetic counseling for risk assessment and to inform family planning.

With the emergence of targeted gene therapy, the role of broader testing should be reevaluated. An argument can now be made to offer testing to all patients with ALS. The frequency of pathogenic variations in sporadic disease is not insignificant, and these patients may eventually be eligible for gene-based therapies currently in development (TABLE 11-4[47-52]). Genetic testing should also be considered for patients younger than 50 years and for patients with ALS-FTD.[53]

PATHOPHYSIOLOGY

We have only a partial understanding of the pathophysiology of ALS, and multiple molecular pathways are likely involved. The rapid discovery of new ALS genes over the past 15 years has provided important insights into the mechanisms of disease. Known pathogenic variations cause disruptions in important pathways, including RNA processing, protein stability and homeostasis, and cytoskeletal function.[54] These mechanisms may overlap and can be associated with many downstream abnormalities, such as protein aggregation, neuroinflammation, and mitochondrial dysfunction.[55] The pathophysiology of ALS thus appears to involve a complex interplay of multiple mechanisms.

MANAGEMENT

The management of ALS is multifaceted. Several disease-modifying treatment options offer a modest benefit on progression or survival. Multidisciplinary care in specialized clinics is essential to address the varied needs of patients with ALS. American Academy of Neurology (AAN) quality measures for care of patients with ALS, updated in 2023, emphasize the importance of multidisciplinary care and now incorporate options for telemedicine services for this patient population.[56]

Disease-Modifying Therapy

Three disease-modifying medications are available for the treatment of sporadic ALS in the United States and Canada, and one drug has been approved for the

TABLE 11-4 **Recent and Ongoing Antisense Oligonucleotide Trials in Amyotrophic Lateral Sclerosis**

Target gene	Medication	Trial name	Phase	Reference
SOD1	Tofersen (BIIB067)	VALOR	Postapproval	US Food and Drug Administration (FDA)[47]
***SOD1* (Asymptomatic)**	Tofersen (BIIB067)	ATLAS	3	NCT04856982[48]
C9orf72	IONIS-C9 (BIIB078)	245AS101	1	NCT03626012[49]
C9orf72	WVE-004	FOCUS-C9	1-2	NCT04931862[50]
ATXN2	ION541 (BIIB105)	275AS101	1-2	NCT04494256[51]
FUS	Jacifusen (ION363)	ION363-CS1	3	NCT04768972[52]

treatment of *SOD1*-associated ALS. All three agents have a relatively modest effect on the course of the disease, resulting in either slowed progression of symptoms or prolonged survival or both. When introducing these options to recently diagnosed patients, it is important to be clear that the disease will, unfortunately, continue to progress even after treatment is started.

Riluzole is an oral inhibitor of glutaminergic excitotoxicity that was approved by the FDA more than 25 years ago. An initial placebo-controlled trial revealed a small but significant (12%) increase in survival in patients taking riluzole versus placebo at the end of the placebo-controlled period (median, 573 days).[57] A follow-up trial revealed an increased survival rate of 7% in patients taking riluzole at 18 months compared with placebo.[58] Review of available trial data revealed a median prolonged survival of 3 months,[59] and a more recent review of real-world evidence suggested an even greater survival benefit of 6 to 19 months.[60] Riluzole is dosed orally at 50 mg 2 times a day and is typically well tolerated, although some patients may experience gastrointestinal discomfort, dizziness, increased transaminase levels, and fatigue. Neutropenia is a rarer adverse effect. Patients taking riluzole should have their liver function tests measured monthly for the first 3 months and then every 3 months thereafter.

Edaravone is a free-radical scavenger that has been shown to modestly slow functional decline in a subset of patients with ALS. An initial 24-week trial did not reveal a statistically significant effect on disease progression, as measured by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score.[61] However, a subsequent post hoc analysis revealed a significant benefit in a subset of patients with a disease duration less than 2 years, preserved respiratory function (ie, forced vital capacity [FVC] at least 80% of predicted), and a score of at least 2 on all ALSFRS-R items. A follow-up, 24-week trial with inclusion criteria to match the post hoc analysis revealed a statistically significant reduction in decline (33%) as measured by the ALSFRS-R.[62] These initial trials suggest that the benefit of edaravone is greatest for patients earlier in the course of the disease and with preserved respiratory function. Questions have also been raised regarding the role of treatment for longer than 6 months. A post hoc analysis from an open-label extension study involving patients from the second phase 3 trial suggested sustained benefit in ALSFRS-R decline in patients who continued taking edaravone for 48 weeks compared with the projected decline for a placebo.[63] However, a subsequent prospective multicenter cohort study did not reveal a benefit of edaravone over standard care for patients treated for a median of 13.9 months.[64] Patients receiving IV edaravone may experience injection site reactions. Other reported adverse effects include gait disturbance and headaches.

In May 2022, the FDA approved an oral form of edaravone, which follows the same dosing schedule as the IV medication.[65] This formulation can also be administered via a feeding tube. In the initial cycle, oral edaravone is dosed at 105 mg (5 mL) daily for 14 days, followed by a 14-day drug-free period. In all subsequent cycles, 105 mg (5 mL) is administered daily for 10 days within a 14-day period, followed by a 14 day drug-free period.

A coformulation of sodium phenylbutyrate and tauroursodeoxycholic acid administered orally daily has recently been introduced as a disease-modifying therapy for ALS in the United States and Canada. In a phase 2 trial, patients with definite ALS with onset of symptoms within 18 months receiving sodium

KEY POINT

- **Genetic testing should be offered to all patients with a family history of ALS and to those with comorbid frontotemporal dementia. There will likely also be a role for more routine testing in all patients with ALS given the frequency of pathogenic variations in sporadic disease and the ongoing development of gene-based therapies.**

phenylbutyrate and tauroursodeoxycholic acid experienced a slower functional decline than patients taking a placebo for more than 24 weeks.[66] A subsequent analysis revealed that patients who started taking sodium phenylbutyrate and tauroursodeoxycholic acid at baseline in the phase 2 trial had a 4.8-month longer median survival compared with placebo.[67] In addition, further analyses adjusting for treatment crossover in the original trial suggested an even greater survival benefit when compared with the intention-to-treat analysis (10.6 months versus 6.9 months longer than placebo subgroups, respectively).[68] This medication received approval from the FDA in 2022 and conditional approval from Health Canada.[47,69] A larger, phase 3 trial has been initiated in the United States and Europe.[70]

The prospect of stem cell therapy has raised hope for neuroprotection and tissue repair in an otherwise degenerative disease. An initial phase 2 trial of mesenchymal stem cell–neurotrophic factor cells in patients with ALS met its primary safety end point.[71] Although the rate of disease progression was similar for treatment and placebo groups, in a subgroup of patients with rapid progression, the rate of progression was improved at earlier time points. A follow-up phase 3 trial did not reveal a significant difference in progression between patients who received three intrathecal mesenchymal stem cell–neurotrophic factor treatments versus those given a placebo.[72] However, improvements were observed in CSF markers of inflammation, neurodegeneration, and neurotrophic factor support in patients receiving the therapy. A subsequent erratum reported that participants with milder disease (an ALSFRS-R score of at least 35) receiving mesenchymal stem cell–neurotrophic factor cells progressed an average 2 points less on the ALSFRS-R compared with those in the placebo arm.[73]

Gene-based therapies for patients with known variations have received increasing attention recently. In a phase 1-2 trial of an antisense oligonucleotide (ASO) to *SOD1* (tofersen), patients who received five treatments over 12 weeks had a significant decrease in CSF *SOD1* concentration.[74] In a subsequent phase 3 trial, there was no significant change in disease progression as measured by change on the ALSFRS-R at 28 weeks between patients taking tofersen versus those taking a placebo.[75] However, treatment was associated with a reduction in CSF *SOD1* and neurofilament light chains, and extension phase studies are examining the responses in earlier versus delayed initiation. Tofersen was recently approved by the FDA through its accelerated approval pathway for the treatment of patients with *SOD1*-associated ALS. Other potential gene-based therapies for ALS include an antisense oligonucleotide to *FUS* (ION363) that was recently shown to reduce protein levels in the brain and spinal cord and delay motor neuron loss in a mouse model. Repeated intrathecal infusions of ION363 in a single patient with *FUS*-associated ALS were reported to result in lower wild-type and mutant protein levels in the central nervous system and a decreased burden of abnormal protein aggregates on autopsy.[76]

Symptomatic and Supportive Care

ALS is a complex disease with varied clinical manifestations. Close monitoring and timely management of respiratory weakness, bulbar function, and nutritional status are necessary to optimize prognosis and quality of life. Treatment of bothersome symptoms such as muscle cramps and sialorrhea is also an important part of patient care.

RESPIRATORY CARE. Patients should be screened early and frequently for symptoms of respiratory muscle weakness, including dyspnea, orthopnea, excessive daytime fatigue, and morning headaches. Symptom review and pulmonary tests, including FVC, slow vital capacity, or overnight oximetry, should be performed at the time of diagnosis and every 3 months thereafter.[77]

Noninvasive ventilation results in prolonged survival and improved quality of life in patients with respiratory involvement.[78,79] The AAN practice parameter for ALS suggests that noninvasive ventilation should be started when vital capacity is less than 50%, sniff nasal pressure is worse than -40 cm H_2O, maximum pressure is worse than -60 cm H_2O, or in the presence of orthopnea or abnormal nocturnal oximetry.[80] Emerging evidence suggests benefits from even earlier initiation of noninvasive ventilation.[81] This may be particularly important if there is any interval decline between the timing of the pulmonary function test and the actual initiation of noninvasive ventilation. More recent Canadian Best Practice Recommendations suggest initiation of noninvasive ventilation at an FVC of 65% of predicted and provides a practical approach to the monitoring and management of respiratory insufficiency (**FIGURE 11-2**).[77]

Patients with ALS also commonly experience difficulty with secretions and airway clearance. Cough augmentation can begin with lung volume recruitment techniques. Mechanical insufflation-exsufflation with cough augmentation should be used when cough peak flow is less than 270 L/min (according to the Canadian Best Practice Recommendations and AAN guidelines[77,80]). Mechanical insufflation-exsufflation can be performed twice daily at baseline and more frequently during acute respiratory infections.

With ongoing progression of respiratory weakness, invasive mechanical ventilation via tracheostomy can be considered. The introduction of invasive mechanical ventilation can significantly prolong survival, and the decision to

KEY POINT

- Disease-modifying therapies for sporadic ALS include riluzole, edaravone, and the coformulation of sodium phenylbutyrate and tauroursodeoxycholic acid. All these agents result in modestly slowed progression, prolonged survival, or both.

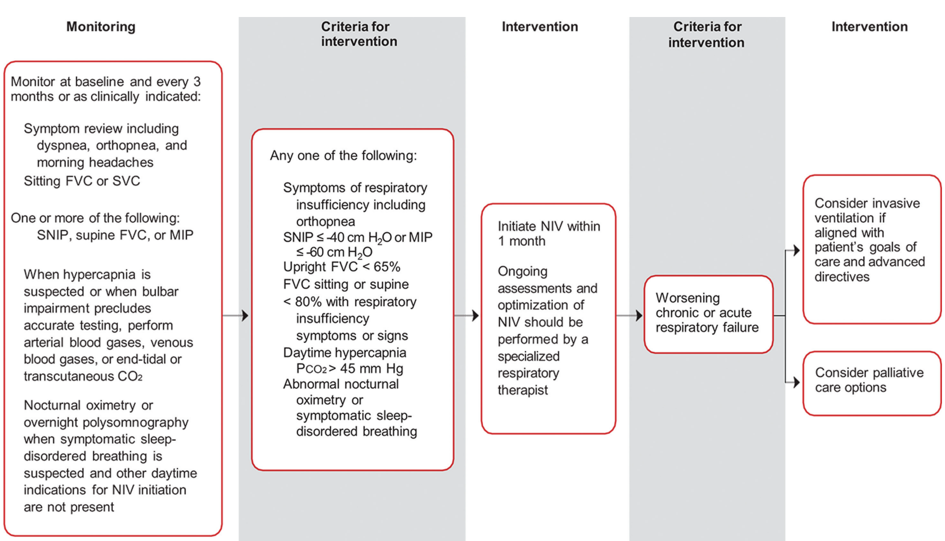

FIGURE 11-2

Management algorithm for respiratory muscle weakness in amyotrophic lateral sclerosis (ALS).
FVC = forced vital capacity; H_2O = water; MIP = maximal inspiratory pressure; NIV = noninvasive ventilation; Pco_2 = partial pressure of carbon dioxide; SNIP = sniff nasal inspiratory pressure; SVC = slow vital capacity.
Modified with permission from Shoesmith C, et al, CMAJ.[77] © 2020 Joule Inc.

KEY POINTS

- Noninvasive ventilation improves quality of life and survival in ALS and should be initiated at a forced vital capacity of 50% or possibly earlier.
- Insertion of a gastrostomy tube should be considered in patients with significant weight loss or dysphagia. Placement should ideally take place before the forced vital capacity is 50%.
- Despite the development of staging and prognostic models, accurate prediction of ALS progression remains challenging.

pursue this intervention should involve careful consideration of quality of life, personal factors such as religious beliefs, and the realities of increased care burden. In North America, less than 5% of patients with ALS ultimately choose to pursue invasive mechanical ventilation, although this number varies significantly by country and may be as high as 38% in Japan.[82]

BULBAR FUNCTION AND NUTRITION. Weight loss due to dysphagia, weakness, atrophy, and hypermetabolism occurs in more than 50% of patients, and poor nutritional status may predict shorter survival.[83-85] Although nutritional supplementation is effective for weight stabilization or gain in ALS, high-quality evidence is limited regarding the benefit of dietary intervention for prolonging survival or slowing disease progression.[86]

Treatment can begin with dietary modification. However, placement of a gastrostomy tube for enteral feeding should be considered in any patient with weight loss or significant swallowing difficulties. Available evidence suggests that gastrostomy tube placement can prolong survival in ALS.[86,87]

The prospect of gastrostomy tube insertion should be introduced early in the course of management to facilitate treatment decisions in advance of any significant nutritional or respiratory decline. In addition to dysphagia and weight loss, worsening respiratory status should prompt timely consideration of referral for gastrostomy tube insertion. The current AAN and recent Canadian guidelines suggest that referral for a gastrostomy tube should occur when the FVC is approaching 50% predicted.[77,80] However, an FVC less than 50% does not necessarily preclude gastrostomy tube insertion, particularly if respiratory status is monitored and managed periprocedurally.[77] The use of noninvasive ventilation during the procedure may improve safety.[88]

OTHER SYMPTOMATIC AND SUPPORTIVE CARE. Patients with ALS should be followed regularly in a multidisciplinary clinic equipped with a team of allied health care providers to address the myriad issues that arise during the course of disease. This should include care for swallowing and nutrition, mobility, activities of daily living, respiratory function, cognition, and medical management. Palliative care providers can play a particularly important role in end-of-life care. There is clear evidence that multidisciplinary care can improve survival and quality of life for patients with ALS.[89-91]

ALS is associated with several motor and nonmotor symptoms that can cause significant morbidity, and management of these issues is a cornerstone of postdiagnosis care (TABLE 11-5). For more information, refer to the article, "Multidisciplinary Clinics in Neuromuscular Medicine" by Kelly Gwathmey, MD, and Terry D. Heiman-Patterson, MD,[92] in this issue of *Continuum*.

PROGNOSIS AND STAGING

Prognostication can be challenging because of the wide variability in phenotypic presentation and rate of progression. Patients will often ask what stage they are in. The King's staging system classifies patients into four categories based on the sequential involvement of body regions and the need for respiratory or swallowing support.[93] The ALS Milano-Torino staging defines six stages of disease based on ALSFRS-R scores in a subset of four scale domains.[94] Patients progress through stages 0 to 5 based on the number of functional domains involved (with stage 5 indicating death). Both staging

systems may provide some prognostic information, although they are not widely used in clinical practice.[95] The Personalized European Network for the Cure of ALS (ENCALS) survival model was developed to provide personalized prognostic information for patients with ALS.[96] Eight clinical predictors, including age at onset, time to diagnosis, rate of ALSFRS-R progression, FVC, bulbar onset, revised El Escorial criteria definite ALS diagnosis, FTD, and *C9orf72* expansion, were shown to accurately categorize patients into five survival groups ranging from very short (predicted median survival, 17.7 months) to very long (predicted median survival, 91.0 months). However, despite such efforts, accurate prognostication remains a significant challenge for clinicians.[97]

OTHER MOTOR NEURON DISEASES

Although ALS is decidedly the most common motor neuron disease, several less common conditions in the category bear mentioning. Recognition of these other diagnoses is critical to inform treatment and provide patients with accurate prognostic information. Several of these conditions are discussed in this section. Spinal muscular atrophy is also a relatively common motor neuron disease, and the advent of gene-based, disease-modifying therapies has helped diagnose a growing proportion of adult patients. For more information on this topic, refer to the article "Spinal Muscular Atrophy" by Maryam Oskoui, MD, FAAN, and Laurent Servais, MD, PhD,[98] in this issue of *Continuum*.

Kennedy Disease

Also known as *spinobulbar muscular atrophy*, Kennedy disease is an X-linked disorder resulting from a CAG trinucleotide expansion in the androgen receptor gene. Affected boys and men can present from the second to sixth decade of life

Symptomatic Management in Amyotrophic Lateral Sclerosis TABLE 11-5

Symptom	Management options
Sialorrhea	Atropine (sublingual), amitriptyline, glycopyrrolate; botulinum toxin injection to salivary glands; radiation; scopolamine patch
Thick secretions	Mucolytics (eg, acetylcysteine, guaifenesin/pseudoephedrine), cough augmentation; hydration
Laryngospasm	Lorazepam as needed, baclofen
Pseudobulbar affect	Dextromethorphan-quinidine, selective serotonin reuptake inhibitor (SSRI)
Dysarthria and impaired communication	Assistive devices, voice banking
Spasticity	Baclofen, tizanidine, botulinum toxin injections to affected muscle groups
Muscle cramps	Baclofen, mexiletine, levetiracetam, carbamazepine, phenytoin, stretching
Depression	SSRI, psychiatry consultation
Muscle weakness and functional decline	Bracing (eg, ankle-foot orthotics), mobility aids including power wheelchair, home occupational therapy assessment

with a combination of symptoms related to motor neuronopathy, sensory neuronopathy, and endocrine dysfunction (CASE 11-3). The most common presenting symptom is lower limb weakness, although examination usually reveals upper limb involvement as well.[99,100] Proximal muscles are often affected early. Facial weakness with associated perioral fasciculations may also be seen, and many patients develop dysarthria and dysphagia. A high-frequency postural tremor is seen in the upper limbs as well. The serum creatine kinase is often increased at greater than 1000 U/L, which may initially cause suspicion for myopathy.

Gynecomastia is a common and early clinical sign, highlighting the importance of a detailed examination. Other features of androgen insensitivity may include testicular atrophy and reduced fertility, but many patients present after they have already had children. Although the motor and endocrine features typically dominate the clinical picture, manifestations of an associated sensory neuronopathy are also present.[101] Patients may endorse paresthesia and numbness in the distal extremities, and sensory amplitudes are often decreased on electrophysiologic testing.[102]

Progression is typically gradual; some patients require the use of a wheelchair later in life. Dysphagia may also progress, at times necessitating the insertion of a gastrostomy tube. Life expectancy is normal, although there may be an increased risk of aspiration and choking.[103] No disease-modifying therapies are available for Kennedy disease.

CASE 11-3

A 38-year-old man presented to the EMG laboratory with a history of cramping and weakness in his thighs with an associated increased serum creatine kinase between 2000 U/L and 3000 U/L. He had difficulty rising from a seated position and going up stairs. He felt that his right leg was weaker than his left. He denied any weakness or cramping in his upper limbs, bulbar weakness, or shortness of breath. His examination revealed mild bilateral facial weakness, moderate weakness of proximal arm and leg muscle with milder weakness in distal muscles, and absent reflexes in his legs. He was also noted to have mild gynecomastia. MRI of his brain and whole spine was unremarkable.

Needle EMG revealed features of active and chronic denervation spanning cervical, thoracic, and lumbosacral muscles. In addition, nerve conduction studies were suggestive of a generalized, sensory-predominant peripheral neuropathy.

COMMENT

Genetic testing revealed a trinucleotide (CAG) expansion in exon one of the androgen receptor gene on chromosome X, compatible with a diagnosis of Kennedy disease. This patient presented with classic features of this condition, including facial and proximal limb weakness, gynecomastia, and increased creatine kinase. The abnormal sensory responses on nerve conduction studies reflected the concomitant ganglionopathy associated with Kennedy disease.

Monomelic Amyotrophy

Monomelic amyotrophy (also known as *Hirayama disease*) is characterized by the onset of unilateral or asymmetric weakness and atrophy of the upper limbs. The disease presents almost exclusively in boys and men in their late teens and early twenties, and patients are often of Asian descent.[104]

In approximately 90% of patients, weakness and atrophy begin and predominate in the hand and forearm muscles, often with preferential medial or ulnar involvement. A minority of patients have more significant proximal involvement. Sensory function is spared, and the affected hand may also have an irregular tremor. Symptoms progress over 1 to 5 years and then plateau, with almost 40% achieving stability by 1 year.[105] O'Sullivan-McLeod syndrome is a considerably rarer LMN syndrome with restricted upper limb involvement that can progress for up to 20 years.[106]

MRI of the cervical spine can reveal focal cord atrophy in lower cervical segments, asymmetric flattening of the cord, T2 hyperintensity in the anterior horns, and detachment of the posterior dura from the lamina. Neck flexion sequences are particularly useful and can reveal anterior displacement of the dural sac with further cord compression and prominence of the epidural venous plexus.[107] These characteristic findings support the suspected pathophysiology of dynamic, focal cord compression and ischemia. In affected patients, there is proposed dysplasia of the dural sac resulting from discordant spinal cord and spinal canal length,[108] occurring with growth during puberty. The adjacent dura are consequently tight and stretched and undergo an anterior shift with neck flexion, leading to compression of the anterior cord against the posterior aspect of the vertebrae. This mechanism explains why the disease is often seen in late adolescence and is typically self-limited.

The mainstay of treatment is supportive care, and patients may benefit from physiotherapy and a conservative exercise program once the condition has stabilized. Some evidence supports the use of a cervical collar earlier in the course of disease.[109,110] However, compliance is often an issue, because many patients will not tolerate wearing a collar regularly for months or years at a time. More rarely, surgical intervention may be a consideration in severe and progressive cases.[111]

Postpolio Syndrome

Postpolio syndrome (PPS) warrants mention in this discussion, because it can bear a striking resemblance to LMN-dominant ALS. Patients with postpolio syndrome present an average of 35 years after initial infection with new, progressive weakness after a prolonged period of stability.[112] In principle, weakness should involve muscle groups affected in the initial infection. However, if prior involvement was subclinical, patients may present with what appears to be new weakness in previously unaffected muscles. Other associated features include pain, generalized fatigue, and worsening muscle atrophy. More rarely, some patients will also experience bulbar and respiratory symptoms.

Postpolio syndrome is thought to result from delayed motor unit dropout, due to natural aging, metabolic stress, and possibly persistent inflammation, superimposed on the previous motor neuron loss sustained in the original infection.[113]

The recognition of postpolio syndrome can be straightforward when there is a clear history of a prior paralytic infection. However, some patients may have

KEY POINTS

- **Kennedy disease is an X-linked motor neuron disease with associated endocrine features (such as gynecomastia), increased serum creatine kinase, and concurrent sensory neuronopathy.**

- **Monomelic amyotrophy is a lower motor neuron disease with asymmetric upper limb involvement that progresses for 1 to 5 years and typically affects males in late adolescence. The workup should include a cervical spine MRI with flexion sequences.**

limited knowledge of their childhood medical history. Moreover, very mild, chronic, and well-compensated weakness may go unnoticed. In these cases in which a prior diagnosis of polio is unclear, helpful clues can include a history of mysterious childhood febrile illnesses and suspicious clinical features such as limb-length discrepancy or foot deformities. Needle EMG typically reveals large motor unit action potentials (reflecting very chronic denervation and reinnervation) and reduced recruitment, as well as abnormal spontaneous activity in the form of fibrillation potentials. Management of postpolio syndrome is mainly supportive, including treatment of associated symptoms.

CONCLUSION

ALS remains a devastating, progressive, and terminal condition with relatively limited treatment options. The presentation is heterogeneous and prognosis is variable, and the diagnosis of ALS is still clinical. Emerging disease-modifying therapies provide modest benefit in slowing progression and prolonging survival, and the advent of gene-based therapies offers hope for patients with familial ALS. Clinicians must also be familiar with mimics of ALS and other less-common motor neuron diseases to ensure accurate diagnosis.

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REVIEW ARTICLE

Spinal Muscular Atrophy

By Maryam Oskoui, MD, FAAN; Laurent Servais, MD, PhD

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

VIDEO CONTENT AVAILABLE ONLINE

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Address correspondence to Dr Maryam Oskoui, Pediatric Neurology, Montreal Children's Hospital, 1001 Decarie Blvd, Ste B.05.2916, Montreal, Quebec, H4A 3J1, Canada, maryam.oskoui@mcgill.ca.

RELATIONSHIP DISCLOSURE:
Dr Oskoui has a noncompensated relationship as a member of the medical and scientific advisory committee with Muscular Dystrophy Canada that is relevant to American Academy of Neurology (AAN) interests or activities and has received personal compensation in the range of $500 to $4999 for serving as a member of the board of directors for the Association des Neurologues du Québec. The institution of Dr Oskoui has received
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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Oskoui and Servais discuss the unlabeled/investigational use of celecoxib, E1v1.11, flunarizine, moxifloxacin, reldesemtiv rigosertib, salbutamol, and securinine for the treatment of spinal muscular atrophy.

ABSTRACT

OBJECTIVE: **This article provides a comprehensive overview of the diagnostic assessment and treatment of individuals with spinal muscular atrophy (SMA) due to homozygous deletions of *SMN1*.**

LATEST DEVELOPMENTS: **In recent years, most states have incorporated SMA in their newborn screening panel. To provide the earliest diagnosis possible after symptom onset, vigilance is needed for births in states without newborn screening for SMA and when compound heterozygotes are missed by newborn screening programs. Supportive care for respiratory, nutritional, and orthopedic health impacts outcomes and is the cornerstone of care. Adaptive equipment, including assistive home technology, enables affected individuals to gain autonomy in their daily activities. Pharmacologic treatments approved by the US Food and Drug Administration (FDA) include three drugs that increase deficient survival motor neuron protein levels through *SMN1*- or *SMN2*- directed pathways: nusinersen, onasemnogene abeparvovec, and risdiplam. Efficacy for these trials was measured in event-free survival (survival without the need for permanent ventilation) and gains in functional motor outcomes. Earlier treatment is most effective across all treatments.**

ESSENTIAL POINTS: **The diagnostic and therapeutic landscapes for SMA have seen dramatic advancements in recent years, improving prognosis. Optimized supportive care remains essential, and vigilance is needed to define the new natural history of this disease.**

INTRODUCTION

The spinal muscular atrophies (SMAs) encompass a group of inherited disorders that cause degeneration of anterior horn cells. The most common of these disorders is 5q SMA, caused by a deletion or variation in the survival motor neuron 1 (*SMN1*) located on chromosome 5q, leading to low levels of expression of the survival motor neuron (SMN) protein. 5q SMA is the second most common autosomal recessive disorder in childhood next to cystic fibrosis, with a live birth incidence of 1 in 10,000.[1] The carrier frequency for *SMN1* gene variations is highest in White and Asian populations (around 1 in 50) and lowest in Black (1 in 100) and Hispanic (1 in 76) populations, with a de novo variation rate of 2%.[1] The gene was localized to 5q13.2 in 1990,[2,3] nearly 100 years after the first clinical description in 1891 in a series of articles by Guido Werdnig in Austria and Johann Hoffmann in Germany.[4,5] The *SMN1* gene was finally identified in 1995, rapidly advancing our understanding of the disease pathophysiology and enabling animal models,

high throughput drug screening, and a successful drug development program.[6] This shift from an untreatable, devastating, and often fatal disease to a treatable and even preventable disease has created meaningful improvements in outcomes and several clinical challenges, with learning opportunities for other neurologic disorders. Challenges include trial design when a placebo arm is clinically unacceptable and, in some subgroups, unethical; rapid implementation of newborn screening; development of responsive and meaningful outcome measures, crowd-funding,[7] and lottery systems.[8] for drug access; and navigating shared decision making when treatment uncertainty remains. This article provides a comprehensive overview of the diagnostic assessment and treatment for individuals with 5q SMA.

GENETICS AND PATHOPHYSIOLOGY

Individuals with 5q SMA present with progressive muscle weakness and atrophy. About 95% of cases are due to homozygous deletions in *SMN1,* leading to loss of function of the SMN protein.[1] 5q SMA is diagnosed by genetic testing, which usually demonstrates homozygous deletion of exon 7, exon 8, or both, in the *SMN1* gene. In 5% of symptomatic individuals, a compound heterozygous state is present. The SMN protein is expressed in all tissues and is involved in various aspects of RNA metabolism via its role in the assembly of the spliceosome. It also plays a role in cell signaling, endocytosis, autophagy, and DNA repair.[9] SMN protein expression is highest in late fetal and early postnatal development.[10] Motor neurons are most susceptible to low levels of expression. In animal models, SMA may present with a non–motor neuron–related phenotype.[11] This seems true only in the most severe cases in humans,[12–14] and the clinical significance of non–motor neuron involvement in humans with a milder phenotype remains to be established as reports of possible dyslipidemia and osteoporosis can also be found in children with severe immobility.

Humans have two forms of the *SMN* gene on chromosome 5q: telomeric *SMN1* and centromeric *SMN2*. *SMN1* produces a full-length mRNA, which encodes the functional SMN protein. *SMN2* is identical to the *SMN1* gene except for five nucleotide differences, of which four are silent, but a critical cytosine to tyrosine substitution results in the exclusion of exon 7 during splicing of the pre-mRNA in most of the transcripts. The SMN protein that results from this transcript is nonfunctional and is quickly degraded. The few *SMN2* mRNA transcripts in which exon 7 has not been spliced will produce functional SMN protein but in a reduced amount. Therefore, the phenotype in patients with SMA is driven by the number of *SMN2* gene copies; a larger copy number is associated with milder phenotypes (**FIGURE 12-1**).[15] In addition, other disease modifiers have been described, mostly leading to attenuated phenotypes. The most common, although still relatively infrequent, disease modifier is a variation in *SMN2* leading to a larger proportion of the full-length transcript. Some of the discrepancy between the copy number and phenotype is because the copy number is not standardized by a protective variation in *SMN2* or by rare genetic modifiers.[16]

The absence of functional SMN protein leads to motor neuronal death. Levels of phosphorylated neurofilaments, a well-established biomarker of neuronal destruction, are dramatically increased at birth in babies with two copies of *SMN2* even before symptom onset and mildly increased in babies with three copies, with a rapid decline over time that attests to the rapid destruction of the

KEY POINTS

- The birth incidence of spinal muscular atrophy has a wide variability although it remains a rare disorder, with approximately 1 in 10,000 births affected.

- The carrier frequency for spinal muscular atrophy is estimated to be as high as 1 in 50 individuals in some populations.

- 5q spinal muscular atrophy is diagnosed by genetic testing which usually demonstrates homozygous deletion of exon 7, exon 8, or both, in the *SMN1* gene. In 5% of symptomatic individuals, a compound heterozygous state is present.

- Survival motor neuron protein is expressed in all cells with highest expression in late fetal and early postnatal development; however, motor neurons are most susceptible to low levels of expression.

pools of motor neurons.[17] The degeneration of motor neurons leads to neuromuscular junction dysfunction and secondary muscle atrophy.[18] In animal models, the absence of the SMN protein in other tissues also contributes to the phenotype, as mice with SMN rescue delivered only in the central nervous system have a shorter lifespan and less weight gain than mice in which the SMN protein has been restored in the entire body.

CLINICAL PRESENTATION

The clinical presentation and the phenotypic spectrum of SMA have changed with the availability of disease-modifying therapies and establishment of newborn screening programs worldwide. The previously most widely accepted clinical classification scheme (**TABLE 12-1**[19]) was established in 1992 at the International SMA Consortium meeting and revised in 2015.[20,21] The spectrum of SMA phenotypes was determined primarily by the highest motor milestone achieved and was associated with prognostic indicators such as expected motor development regression and life expectancy without supportive care. However, since the availability of disease-modifying therapies, the future prognosis of treated patients is largely unknown.

SMA type 0 and SMA type 1A are the most rare and severe clinical phenotypes characterized by the onset of muscle weakness in utero. Infants are symptomatic at birth or in the first week of life and present with areflexia and hypotonia. Early death by respiratory failure is inevitable without supportive care. In the most severe cases, cardiac and brain malformations have been reported.

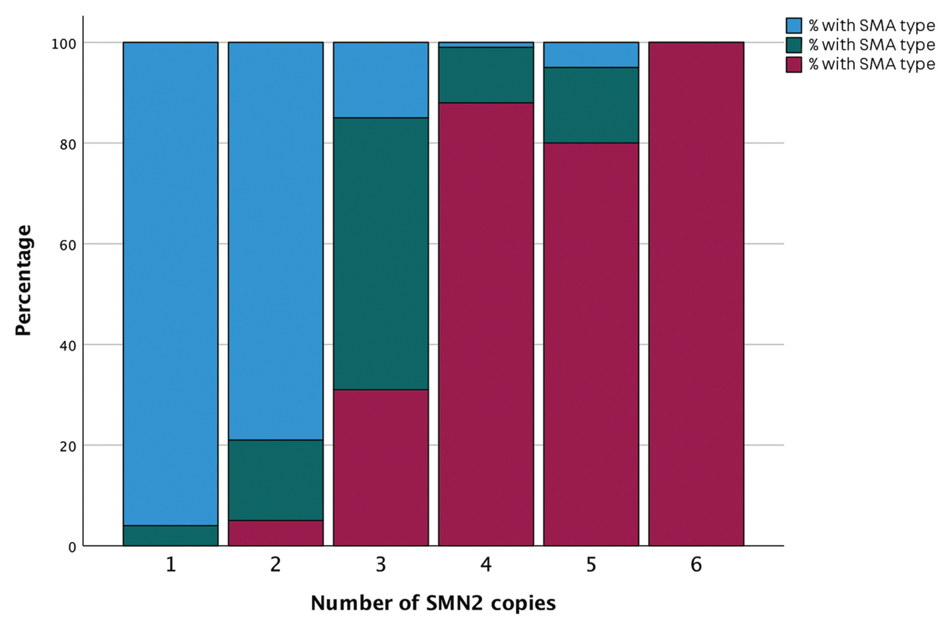

FIGURE 12-1

Percentage of patients with spinal muscular atrophy (SMA) types 1, 2, and 3 by *SMN2* copy numbers, illustrating the dose-dependent effect of *SMN2* copy numbers on clinical phenotype. Lower numbers of *SMN2* copies are associated with earlier and more severe presentations (SMA type 1), and larger copy numbers are associated with later and milder phenotypes (SMA type 3).

SMN = survival motor neuron.

Data from Calucho M, et al, Neuromuscul Disord.[15]

Infants with SMA type 1B appear asymptomatic at birth, but motor neuron loss is likely to have started in utero, especially in those with two copies of *SMN2*. Infants develop symptoms in the first 3 months of life, often noted by parents as reduced movements in the lower limbs. They have significant axial hypotonia, proximal weakness, and areflexia on examination; never achieve the ability to stay seated; and have a weak cry, tongue fasciculations, and often chest wall weakness with paradoxical breathing. Their bulbar weakness leads to feeding difficulties and a high risk of aspiration. Without supportive care, their chest wall development is altered, and they develop a bell-shaped thorax and respiratory failure with an event-free survival median age of 11.9 months (interquartile range, 7.0 to 22.0).[22]

Infants with SMA type 1C present at an older age (3 to 6 months) and have a similar clinical presentation. Some infants can stay seated when propped for brief periods, but they soon lose this ability. Their event-free survival is longer at 13.6 months (interquartile range, 8.8 to 20.1).[22]

Children with SMA types 2A and 2B achieve the ability to sit independently; however, those with type 2B lose this ability over time. Some children can stand with or without support and crawl, but they do not achieve the ability to walk independently. Parents generally bring them for evaluation at presentation because of motor development impairment or weakness in the lower limbs. On examination, they may have preserved distal reflexes, polyminimyoclonus noted as a fine tremor of fingers that does not interfere with function, and a nasal voice. Bulbar weakness is more pronounced in some, with risk of aspiration and need for ventilatory support. Contractures and scoliosis evolve over time, and the latter can further impact respiratory reserve.

Clinical Subtypes of Spinal Muscular Atrophy[a] **TABLE 12-1**

Spinal muscular atrophy type	Age of onset	Highest motor milestone without disease-modifying treatment	*SMN2* copy number	Life expectancy without disease-modifying treatment or supportive care
0	Fetal	Never rolls or sits	1	<1 week
1A	Fetal	Never rolls or sits	1	<6 months
1B	First 3 months	Never sits	2, 3	<2 years
1C	3-6 months	Never sits	2, 3	<2 years
2A	6-18 months	Sits independently	2, 3, 4	>2 years
2B	6-18 months	Sits independently, able to stand and support weight with assistance, bracing or independently	2, 3, 4	>2 years
3A	<3 years	Walks independently	3, 4	Adult
3B	>3 years	Walks independently	3, 4	Adult
4	>21 years	Walks independently	4, 5	Adult

[a] Modified with permission from Oskoui M, et al.[19] © 2017 Elsevier Inc.

Children with SMA type 3 achieve the ability to walk independently, often defined as walking without support for 10 meters or more. Many can lose this ability over time, and generally survive well into adulthood. Parents seek evaluation for proximal weakness of the lower limbs, and at presentation, children have a positive Gowers sign with often preserved muscle stretch reflexes, as shown in the videos for CASE 12-1.[23] Some children may have polyminimyoclonus or a nasal voice, but these findings are often not present initially. A high index of suspicion is needed for early diagnosis, and these children have the longest delay between symptom onset and diagnosis. Patients with later-onset SMA types 2 and 3 have some metabolic, bone, endocrine, or renal dysfunction, but the clinical significance of these findings is unknown. Whether these systemic manifestations are due to reduced SMN protein expression or are secondary to immobility is unclear.[24]

SMA type 4 refers to individuals with symptom onset after 21 years of age and very slowly progressive proximal limb girdle weakness. Most patients maintain ambulation, although a small proportion can lose this ability in older adulthood. Bulbar and respiratory muscles are usually spared, and scoliosis is less prominent.

Disease-modifying therapies initiated after symptom onset have markedly changed prognosis in individuals with SMA. The event-free survival of infants with SMA type 1 treated before 7 months of age is markedly improved across all three available treatments, with many acquiring the ability to sit independently. However, they maintain significant bulbar weakness and develop scoliosis over time. Children with SMA type 2, especially those treated when younger than

CASE 12-1

A 4-year-old boy presented for evaluation of muscle weakness. His early developmental milestones were within an age-appropriate timeframe. However, by 2 years old, he had frequent falls and difficulty climbing stairs. On examination, proximal symmetric weakness was evident in his arms and legs. A Gowers sign was present. Muscle stretch reflexes were present throughout except at his knees (VIDEO 12-1[23]). Gene testing confirmed the homozygous absence of *SMN1* gene exon 7 and presence of four copies of *SMN2*. By 10 years old, after 2 years of treatment with nusinersen, he remained ambulatory, although he had a waddling gait and was areflexic at his knees, with the remaining muscle stretch reflexes still present (VIDEO 12-2).

COMMENT

The progression of muscle stretch reflex loss in SMA follows a specific pattern of proximal to distal, lower to upper limb, as reported in this case, with patellar areflexia preceding the Achilles and upper limb reflexes. Early recognition of patients with spinal muscular atrophy with preserved or even brisk reflexes at presentation can reduce diagnostic delay and allow earlier treatment initiation. With spinal muscular atrophy newborn screening increasing the known number of presymptomatic patients, clinical vigilance is needed to recognize the earliest clinical manifestation of motor neuron instability.

Modified with permission from Oskoui M, et al, Neurol Clin Pract.[23] © 2020 American Academy of Neurology.

5 years old, have a marked difference in motor development and maintain the ability to stay seated over time, with some gaining the ability to stand. With the availability of newborn screening in most states, incident cases are being detected shortly after birth. Infants with three or four copies of *SMN2* typically are fully asymptomatic at birth; those with two copies of *SMN2* are at higher risk of developing early symptoms, especially if treatment initiation is delayed.[25] The newborn screening experience in Australia has shown that 29% of infants who screen positive for SMA show signs of SMA within the first 4 weeks of life.[26] These early signs can include loss of muscle stretch reflexes and hypotonia. Infants treated presymptomatically have the best prognosis, achieving the ability to walk without support; however, treatment remains disease modifying and not curative. Infants treated presymptomatically, especially those with two copies of *SMN2*, can develop symptoms of proximal weakness, impaired motor development, and bulbar weakness over time. Long-term prognosis beyond 5 years is not yet known, as the first treated cohort continues to be monitored.

KEY POINTS

- **Levels of phosphorylated neurofilaments, a well-established biomarker of neuronal destruction, are dramatically increased at birth in babies with two copies of *SMN2*, even before symptom onset.**
- **Early recognition of patients with spinal muscular atrophy with preserved or even brisk muscle stretch reflexes at presentation can reduce diagnostic delay and allow earlier treatment initiation.**

DIAGNOSTIC EVALUATION

Since the first successful clinical trials of SMA disease-modifying treatments in humans, evidence has consistently shown higher efficacy in patients treated early compared with patients treated late.[27] For instance, patients with early-onset SMA treated with nusinersen during the pivotal phase 3 trial presented with a much better event-free survival if disease duration was less than 13 weeks.[28] In the pivotal trials in later-onset SMA, motor improvement as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE) was much higher in patients treated before 6 years of age.[29] Similar evidence was reported in trials assessing the efficacy of onasemnogene abeparvovec[30] and risdiplam.[31] These findings rapidly led to the design and initiation of trials in presymptomatic infants for nusinersen (NURTURE),[17] onasemnogene abeparvovec (SPR1NT),[32,33] and risdiplam (Rainbowfish).[34] The findings of these trials converge to demonstrate normal motor development in patients who are presymptomatic with three copies of *SMN2* treated before they are 42 days old, regardless of the treatment administered, and in about half of patients with two copies of *SMN2*. In the other half, the motor progress was significantly improved compared with the progress reported in symptomatic patients treated with the same drug. This effect is well demonstrated in CASE 12-2, in which a presymptomatically treated infant with two copies of *SMN2* attains the ability to walk independently but develops proximal weakness over time.

These findings supported the creation of several pilot newborn screening programs in Taiwan[35] (where patients were not treated before symptoms), New York,[36] Belgium,[37] and Germany.[38] Several other pilots and national programs were subsequently developed in Australia,[39] Japan,[40] the United States,[41] Canada,[42] and several European Union (EU) countries.[43] These programs all demonstrate a very high positive predictive and negative predictive value of polymerase chain reaction (PCR) testing for SMA. After optimization of the primers used in the initial programs, very few false-positive cases (in Australia) and one false-negative case have been reported.[44] A second important finding of these newborn screening programs is that only a partial overlap is found between patients identified by newborn screening and presymptomatic patients reported in clinical trials. About 40% of patients with two *SMN2* copies present with symptoms at treatment, and these patients would have been excluded from

presymptomatic trials.[45] Finally, programs that have collected health economic data converged to show a high cost-effectiveness of newborn screening in the context of approved disease-modifying treatments.[46]

Across the United States, 48 states have established a newborn screening program as of September 2022. Despite rapid implementation in several countries, today only a minority of newborns in the world are screened for SMA.[47] In this context, the a priori probability of SMA in a baby with hypotonia and areflexia remains high in infants born in countries where newborn screening was not implemented. Additionally, exceptional false-negative cases, babies for whom parents have refused newborn screening and infants with heterozygous deletions and point variations, can still be identified after symptom onset. The latter account for about 5% of incident cases in locations with newborn screening in place and are thus likely to become increasingly prevalent among patients identified by symptoms. Since early treatment improves outcomes, even in symptomatic patients, medical education of symptoms and clinical signs remains of primary importance, especially with an incidence that is dramatically lower in the context of newborn screening, and that could lead to a decreased awareness about SMA. Patients with SMA type 2 or 3 can have preserved reflexes at the time of first symptom presentation, and a high index of suspicion is needed for SMA since it is now a disorder with disease-modifying treatments. Conveying the message that the absence of homozygous deletion of *SMN1* exon 7 does not rule out SMA in patients with suggestive clinical presentation is also key to reducing diagnostic odysseys, which remains significant even for SMA type 1.[48] Individuals who are compound heterozygotes with a deletion of exon 7 in one *SMN1* allele and a point variation in the other allele need additional targeted sequencing for diagnosis.

Neurophysiology testing is no longer required to establish a diagnosis; however, compound motor action potential amplitudes can be an indirect

CASE 12-2

A 22-day-old infant boy was identified by newborn screening to have homozygous *SMN1* deletions and two copies of *SMN2*. He was treated with onasemnogene abeparvovec when he was 43 days old. At the time of treatment administration, very mild clinical signs were observed in his lower limbs, with reduced spontaneous antigravity movement and diminished but preserved reflexes (VIDEO 12-3). He responded well to treatment and met early motor developmental milestones and acquired independent ambulation when he was 11 months old (VIDEO 12-4). Nevertheless, by the time he was 3 years old, clear proximal motor weakness in his lower limbs was observed (VIDEO 12-5).

COMMENT

This case illustrates that patients identified by newborn screening, especially those with two copies of *SMN2*, may nevertheless show subtle clinical signs in the neonatal period, reflecting an already significant loss of motor neurons. The age-appropriate motor development during the first 2 years of treatment does not preclude future clinical progression of the disease, as the demands on motor neurons increase with development.

measure of disease progression across all patients with SMA and may be useful to monitor patients with four copies of *SMN2* in settings where treatment cannot be initiated presymptomatically.[44]

The use of carrier screening, which identifies couples who both have only one copy of *SMN1* exon 7 and have a 25% risk of having an affected child with each pregnancy, is increasing in several countries, including the United States, Belgium, Australia, and countries of the Middle East region, and can also contribute to the dramatic decrease of the incidence of symptomatic presentations. This has already been observed in New York.[36] In Israel, carrier screening has not significantly impacted the incidence of SMA.[49] Outside the social and educational bias in the population that benefits from carrier screening, this method fails to prevent new variation, transmission by silent carrier (carrying two *SMN1* copies on the same chromosome), and pregnancy with someone other than the tested partner.

Shortly after the identification of the first presymptomatic cases, a broad consensus was reached that patients with SMA with two or three copies of *SMN2* should be treated immediately.[50] In the United States, the three drugs approved by the US Food and Drug Administration (FDA) can be used in these infants, but in the EU and Canada, risdiplam is currently only approved in patients older than 2 months. Only one article reported the follow-up of these patients without treatment.[35] As the cohort is small and a large portion of clinical data are missing, evaluating this treatment strategy is difficult.

A Delphi panel initially failed to reach consensus on the treatment of patients with four copies of *SMN2*, which led to insurers declining reimbursement for disease-modifying treatment for these patients in several countries. The same panel reached a consensus 2 years later to treat these patients and published a revised opinion.[51] Emerging evidence from real-world data shows that 4 of 7 of untreated patients with four copies of *SMN2* present with symptoms by 3 years old and that these symptoms are only partially reversible with treatment.[52]

RECOMMENDED CARE

The first recommended best practices for the care of patients with SMA were published in 2007, and these emphasized the importance of multidisciplinary team management, considering the orthopedic, respiratory, digestive, nutritional, and palliative care necessary for optimal outcomes.[53] The second edition was published in 2018 and included additional topics such as medications, acute care, rehabilitation, and other organ involvement.[54,55] Apart from diagnostic recommendations, very few recommendations today are based on a level of evidence above expert consensus. This underlines the need to generate additional high-quality evidence to inform clinical practice. All treatment trials were conducted in patients following these standardized recommendations for care, emphasizing the importance of implementing these care measures alongside disease-modifying treatment. Children with SMA type 1 treated after symptom onset can continue to experience significant respiratory and bulbar weakness and need supportive care.

Outcome Measures

Measuring function in the context of disability is a multidimensional construct, and the International Classification of Functioning, Disability and Health model provides an excellent framework for evaluation. These outcome

KEY POINTS

- **Neurophysiologic testing is no longer required in the diagnostic assessment of spinal muscular atrophy to establish a diagnosis; however, compound motor action potential amplitudes can be an indirect measure of disease progression and useful to monitor in patients with four copies of survival motor neuron type 2 in settings where treatment cannot be initiated presymptomatically.**
- **Shortly after the identification of the first presymptomatic cases through screening programs, a broad consensus was reached that patients with spinal muscular atrophy with two or three copies of *SMN2* should be treated immediately.**
- **Recommended best practices with developmental surveillance and respiratory and nutritional support are the cornerstone of treatment in spinal muscular atrophy.**
- **Measuring spinal muscular atrophy treatment response in clinic should be based on appropriate motor function measures by phenotypes and age, as well as individual goals of care to guide shared decision making.**

measures include the impact of the disease on bodily functions and structures, which is the most commonly measured dimension in SMA, and also the impact on the individual's activities and participation in all areas of life. Both environmental and personal factors will further influence bodily functions and structures, activities, and participation. As a motor neuron disorder with onset during a critical developmental period of the neuromotor axis, the impact of SMA on bodily functions and structures is most often measured by motor function (TABLE 12-2[56-62]). The World Health Organization motor milestones provide the broad categories representing the spectrum of abilities in SMA that

TABLE 12-2 **Functional Motor Outcome Measures**

Name	Scoring	Age and functional status	Functions evaluated	Equipment needed	Duration
Hammersmith Infant Neurological Examination Section 2 (HINE-2)[56]	8 items	2-24 months, any functional status	Head control, sitting, grasping, kicking, rolling, crawling, standing, walking	Does not need special equipment	15 minutes
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)[57]	16 items	Any age, nonsitters	Head control, rolling, gross motor functions of upper and lower limbs, axial strength and tone	Mat, standardized toys in a clinical trial setting (rattle, Sophie the Giraffe, toy phone)	20 minutes
Hammersmith Functional Motor Scale Expanded (HFMSE)[58]	33 items	>2 years, sitters and walkers	Rolling, sitting, lying to sitting, kneeling, kneeling to standing, squatting, jumping, stair climb and descent	Mat, adjustable bench, stairs, tape, and ruler	10-30 minutes
Revised Upper Limb Module[59]	19 items	>30 months, sitters and walkers	Upper limb gross and fine motor functions	Plastic cup, button light, calibration weights, sand weights, pencil, plastic container, and paper	15 minutes
Motor Function Measurement (MFM)[60]	MFM-20: 20 items (2-7 years) MFM-32: 32 items	2-60 years, any functional status	Upper and lower limb gross and fine motor functions, rolling, lying to sitting, sitting to standing, running, hopping	Tennis ball, coins, compact disc, pencil, paper, stopwatch, and other items found in therapy settings	30-45 minutes
6-Minute Walk Test (6MWT)[61]	Distance in meters	>3 years, able to walk independently	Walk as fast as possible along a 25-meter loop for 6 minutes	Clear 30-meter walkway, tape measure, stopwatch, two orange cones, and sticky notes	6 minutes
Timed Up and Go[62]	Time in seconds	>3 years, able to walk independently	Stand from chair, walk 3 meters, return to chair, and sit down	A chair, a clear 3-meter walkway, tape measure, stopwatch	5 minutes

historically defined the clinical classification of the disease. However, these milestones are less responsive to change, especially in older children where the goal of treatment may not be acquisition of new motor milestones but maintenance of acquired skills. Gaining the ability to stay seated without support for a variable duration of time has been used as an objective motor outcome in infants with SMA, especially in those with two copies of *SMN2* who are predicted to develop SMA type 1 and never acquire this ability without treatment. Several motor function assessments have been developed and validated in the SMA population, with natural history cohorts available mostly in the pediatric population (**TABLE 12-2**). Continuous measure of motor activity by wearable sensors has been reported to detect a 6-month change in nonambulatory patients[61] and is now increasingly used in clinical trials (eg, NCT05115110).[63] Several studies have been conducted so far with spine and muscle MRI, but the added value of these techniques remains to be demonstrated.[61]

The impact of care on activities and participation is not as well measured and relies mostly on patient-reported outcomes, as in **CASE 12-3**, in which a 25-year-old woman is treated with risdiplam.

CASE 12-3

An 8-month-old girl with delayed motor milestones was diagnosed with spinal muscular atrophy type 2 (three copies of *SMN2*). She had acquired the ability to sit up by herself before her diagnosis but lost this ability at 4 years old. At 8 years old, nocturnal noninvasive ventilation support was initiated, and she achieved excellent academic performance. She received treatment with risdiplam at 25 years old. At treatment initiation, she presented with a Brooke Upper Extremity Rating Scale score of 3 out of 6, Hammersmith Functional Motor Scale Expanded (HFMSE) of 2 out of 66, and Revised Upper Limb Module of 15 out of 37, and forced vital capacity was 43% predicted. The therapeutic objective was to improve stamina, since she was exhausted after her days at university, and improve distal upper limb function directly impacting daily activities that were meaningful to her. After 1 year of treatment, she reported more strength in her hands, ability to drink a cup filled with a greater volume of tea inside, better stability seated in her wheelchair, ability to start eating uncooked vegetables, ability to write for a longer period, and stamina to perform manual hobbies such as needlepoint even after a full day at the university. No improvement was noticed on the different functional motor scales, which remained stable. Nevertheless, she described these small improvements in bulbar, upper limb function, and endurance as transformative. Innovative methods using wearable sensors helped to quantify motor improvement.[61]

COMMENT

This case illustrates the need for setting realistic individualized treatment goals and expectations and illustrates the gap between individually experienced improvements and quantified functional motor scales (**VIDEO 12-6**). Innovative outcomes and biomarkers are currently being investigated to better quantify these small but important changes.

KEY POINT

- Nusinersen 12 mg administered by intrathecal injection has been approved by the US Food and Drug Administration since 2016 and has demonstrated efficacy across a wide range of spinal muscular atrophy phenotypes.

The Canadian Occupational Performance Measure is a patient-reported outcome measure used to identify and prioritize challenges that restrict children's participation in daily life activities.[64] This measure is obtained by semistructured interviews with the child and their caregiver and focuses on occupational performance in all areas of life, identifying challenges in self-care, leisure, and productivity. Canadian Occupational Performance Measure administration yields two scores: (1) perception of current performance and (2) satisfaction with current performance; each score ranges from 1 (poor performance or lowest satisfaction) to 10 (excellent performance or high satisfaction).

Survival and bulbar function, including feeding, swallowing, and breathing, are other important outcomes to measure. Simple measures of bulbar function include maintaining the ability to swallow and identifying nutrition as primarily oral or via enteral tube. Pulmonary function tests can be performed in older children who can cooperate with the evaluation and have sufficient oromotor control. In infants with SMA who develop bulbar dysfunction and respiratory failure, ventilatory support prolongs survival. The combined endpoint of event-free survival considers surviving without the need for permanent ventilation. Although the definition of permanent ventilation is variable, the clinically accepted construct is the dependence on ventilatory support for most of the day in the absence of a reversible cause such as intercurrent illness.

DISEASE-MODIFYING TREATMENTS

Three disease-modifying treatments are now clinically available for individuals with SMA after demonstrating efficacy in clinical trials (**TABLE 12-3**[17,28,29,31-33,65-67]). These treatments increase full-length SMN protein levels, either by optimizing *SMN2* pre-mRNA inclusion of exon 7 or by introducing the *SMN1* gene copy. Several non-SMN–directed treatments are under development, most to complement the SMN-directed treatments.

Survival Motor Neuron–Directed Treatments

SMN protein deficiency is central in the disease pathophysiology of SMA. The main disease-modifying therapies in SMA therefore aim to increase the levels of SMN protein, principally at the level of motor neurons.

NUSINERSEN. Nusinersen is an antisense oligonucleotide administered intrathecally that modulates the splicing of the *SMN2* pre-mRNA to produce more full-length SMN protein. It was the first disease-modifying therapy approved for use in individuals with SMA and obtained FDA approval in December 2016. Nusinersen dosage on the approved monograph is uniform: 12 mg (5 mL) administered intrathecally, with 4 loading doses administered in the first 2 months of treatment followed by a maintenance dose every 4 months. Renal toxicity, thrombocytopenia, and coagulation abnormalities have been reported with use of other antisense oligonucleotides; therefore a complete blood cell count, coagulation parameters, and quantitative spot urine protein testing are recommended before each intrathecal injection. Insufficient data exist on the risk of teratogenicity during pregnancy or risk with lactation, although preclinical studies have not demonstrated any abnormalities in organogenesis.

Three pivotal trials demonstrate nusinersen's efficacy. The first was ENDEAR, a sham-controlled triple-blind randomized trial that enrolled symptomatic SMA

type 1 infants 7 months or younger who were dosed according to product monograph dosage. Infants with symptoms in the first week of life were excluded.[28] The sham procedure arm terminated early at interim analysis as there was a significant difference in survival between the two groups. The study met its primary endpoints of survival and improvement in motor milestones as measured on the Hammersmith Infant Neurological Examination Section 2. The second pivotal trial was CHERISH, a sham-controlled, triple-blind randomized trial that enrolled children 2 to 12 years old who were able to sit independently but never walked.[29] The inclusion and exclusion criteria restricted enrollment to children without significant contractures that would hinder improvement in motor scores, without severe scoliosis, and without ventilatory or nutritional supplementation. The nusinersen dosage was different from the product monograph, with 4 loading doses administered over 2 months followed by a maintenance dose every 6 months. The final study population of 2- to 9-year-old children met the primary outcome and also ended at interim analysis. Finally, NURTURE was an open-label pivotal trial of nusinersen initiated in the first 6 weeks of life in presymptomatic infants with two or three copies of *SMN2*.[17] A historic comparison group of symptomatic infants was used; however, no true

Survival Motor Neuron–Directed Treatment Pathways for Patients With Spinal Muscular Atrophy — **TABLE 12-3**

Drug	Date of FDA approval, age group	Mechanism of action	Pivotal trials (age range inclusion)	Dose, route of administration, and frequency of maintenance	Main adverse effects
Nusinersen	December 2016, all ages	Antisense oligonucleotide splicing modifier of *SMN2*	ENDEAR[28] (1 week to 7 months), CHERISH[29] (2-12 years), NURTURE[17] (0-6 weeks)	12 mg; intrathecal; 4 loading doses over 2 months, then maintenance every 4 months	Adverse effects related to the lumbar puncture, unknown risk of teratogenicity
Onasemnogene abeparvovec	May 2019, <2 years	*SMN1* gene replacement via AAV9 vector	STR1VE[65,66] (<7 months), SPR1NT[32,33] (0-6 weeks)	1.1×10^{14} vector genomes (vg)/kg patient body weight, IV single infusion	Thrombotic microangiopathy, liver toxicity and acute liver failure leading to death, thrombocytopenia
Risdiplam	August 2020, May 2022,[a] all ages	Small molecule splicing modifier of *SMN2*	FIREFISH[67] (0-7 months), SUNFISH[31] (2-25 years), Rainbowfish (0-6 weeks)	<2 months: 0.15 mg/kg 2 months to <2 years: 0.20 mg/kg ≥2 years and <20 kg: 0.25 mg/kg ≥2 years and ≥20 kg: 5 mg Orally, once daily after a meal	Potential teratogenicity, photosensitivity, diarrhea

FDA = US Food and Drug Administration.
[a] FDA approved in May 2022 for children younger than 2 months old.

natural history of presymptomatic infants with two or three copies of SMA is available. They enrolled a total of 25 infants with a 5-year follow-up. At interim analysis, marked improvements in motor milestones in all infants compared with historical controls were noted. Those with three copies of *SMN2* met their motor developmental milestones within the World Health Organization–appropriate age limits. However, a proportion of infants with two copies of *SMN2* developed proximal weakness and bulbar symptoms over time. Nusinersen is generally well tolerated, although case reports of communicating hydrocephalus have been reported. Most reactions, such as positional headache, are secondary to the lumbar puncture procedure.

ONASEMNOGENE ABEPARVOVEC. Safety and efficacy of a single IV infusion of 1.1×10^{14} vector genomes (vg)/kg of onasemnogene abeparvovec was demonstrated in two open-label, single-arm, single-dose phase III studies using historical control groups.[65,66] The two studies that included patients with SMA type 1 with two copies of *SMN2* who were younger than 6 months differed not only by the localization of the investigation sites (one in the United States, the other in the EU) but also by the inclusion criteria that were more expansive in the EU study, allowing the inclusion of patients with nutritional or respiratory support at baseline.

The co-primary endpoints were event-free survival at 14 months and independent sitting for 30 seconds or longer in the US study and 10 seconds in the EU study at 18 months. Secondary outcomes included the ability to maintain proper growth without nutritional support requirements or swallowing issues and independence of ventilatory support at 18 months. As a consequence of more permissive inclusion criteria in the EU study, the enrollment age in the US study was slightly younger than in the EU trial (mean 3.7 months versus 4.1 months), and the baseline CHOP-INTEND was higher (32.0 versus 27.9 months). Both studies achieved a remarkable event-free survival at 14 months (20 of 22 in the US study, 31 of 33 in the EU study), and the proportion of patients who achieved independent sitting, despite a more stringent definition of sitting (30 versus 10 seconds), was slightly higher in the US study (13 of 22 versus 14 of 33) as was the proportion of infants achieving the ability to maintain growth independently (9 of 22 versus 7 of 33). In both studies, the drug was well tolerated, and the most common drug-related adverse events were pyrexia, increased hepatic transaminase concentrations, and gastroenteritis. One patient presented with hydrocephalus.

Onasemnogene abeparvovec was also studied in an open-label trial (SPR1NT) of patients younger than 42 days with two ($n = 14$)[32] and three ($n = 15$)[33] copies of *SMN2* and presenting with no symptoms at treatment initiation. The objective primary endpoint was the acquisition of an independent sitting position at 18 months of age and standing without support at 24 months of age for patients with two and three copies of *SMN2*, respectively. All patients with two and three *SMN2* copies remained alive, were free of ventilation and nutritional support, and achieved their respective primary efficacy endpoint. Onasemnogene abeparvovec was equally well tolerated as no infant enrolled in SPR1NT experienced a serious adverse event that was considered treatment-related by the investigator, and no new safety signals were identified. These data were broadly reproduced in real-world experience[68,69] and expanded the eligible population in terms of age and weight.

Clinical access to onasemnogene abeparvovec in the United States follows the FDA label for children younger than 2 years old and highlights that efficacy has not been demonstrated in children with advanced disease. The FDA warning emphasizes liver toxicity and acute liver failure leading to death, recommending pretreatment laboratory testing (eg, hepatic aminotransferases with aspartate aminotransferase [AST] and alanine aminotransferase [ALT], total bilirubin, and prothrombin time), as well as monitoring of platelets and troponin-I. AAV9 antibody titers are also measured pretreatment, and patients with a titer above 1/50 are excluded as it could block transmission and constitutes a risk for immune reaction. If any intercurrent illness is present, the infusion should be postponed, and live attenuated vaccines should be avoided to prevent immune system activation and secondary risks associated with this. Systemic corticosteroids equivalent to 1 mg/kg per day of prednisolone are administered to all patients the day before infusion and continued for 28 days with close monitoring of hepatic aminotransferases and liver function. If they have normalized (below twice the upper limit of normal), gradual tapering is initiated after the first month. If liver function abnormalities persist, consulting a pediatric gastroenterologist or hepatologist is encouraged. It is recommended to continue monitoring for at least 3 months. If oral corticosteroids are not tolerated, or if there is significant elevation of hepatic aminotransferases, IV corticosteroids can be used. Cases of thrombotic microangiopathy have also been reported in postmarketing surveillance within the first 2 weeks following infusion, characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. Concurrent immune system activation was identified in some cases.

RISDIPLAM. Risdiplam is an orally administered, systemically distributed small molecule that alters the *SMN2* pre-mRNA splicing to produce more full-length SMN protein. Its efficacy was established in two pivotal trials, obtaining initial FDA approval in August 2020.[67,70] FIREFISH part 2[70] was an open-label phase 3 study using an external comparison group in infants with SMA type 1B born at term and treated between 1 and 7 months. The objective primary outcome of sitting without support for at least 5 seconds after 12 months, as assessed by item 22 of the gross motor scale of the Bayley Scales of Infant and Toddler Development, Third Edition, was reached.[70] The second pivotal trial was SUNFISH part 2, a blinded placebo-controlled phase 3 trial in a broad spectrum of children and young adults 2 to 25 years old with SMA type 2 or 3 who were nonambulatory.[71] Participants were eligible if they were nonambulatory, could sit independently, and had a score of at least 2 in entry item A of the Revised Upper Limb Module (can raise one or two hands to the mouth but cannot raise a cup with a 200-g weight in it to the mouth). Participants (N = 120) were randomly assigned 2:1 to receive risdiplam at a dose of 5 mg (for individuals weighing ≥20 kg [44 lb]) or 0.25 mg/kg (for individuals weighing <20 kg [44 lb]), or daily oral placebo (matched to risdiplam in color and taste). The primary efficacy of change from baseline in the 32-item Motor Function Measurement total score at month 12 was reached. At month 12, the difference between the risdiplam and placebo group in least squares mean change from baseline in 32-item Motor Function Measurement was 1.55 (0.30 to 2.81, $P = .016$) in favor of risdiplam. Participation was not excluded for those on tube feeding or ventilatory support nor for those with severe contractures or scoliosis. A third

KEY POINTS

- **IV onasemnogene abeparvovec shows the highest efficacy if initiated presymptomatically in patients with two or three copies of *SMN2* and has been approved by the US Food and Drug Administration since May 2019 for treatment of children younger than 2 years old.**
- **Risdiplam is an orally administered, systemically distributed molecule approved by US Food and Drug Administration in August 2020 and has demonstrated efficacy across a broad range of phenotypes in patients younger than 25 years old.**
- **There is currently no evidence of efficacy for combining spinal muscular atrophy therapies aimed at increasing survival motor neuron protein production. The additional cost, the burden for patients, and additional risk of adverse effects should be considered in parallel with the absence of evidence of additional benefit from combined therapies.**
- **A shared informed decision process is encouraged when choosing which spinal muscular atrophy disease-modifying therapy to initiate while considering available evidence, patient preferences, and availability of treatments.**

pivotal trial still underway is Rainbowfish,[34] an open-label study in presymptomatically treated infants with either two or three copies of *SMN2*. Interim results were encouraging, showing after 12 months of treatment with risdiplam that most presymptomatic babies met key motor developmental milestones in addition to maintaining the ability to swallow. The evaluation of risdiplam pharmacodynamics in the 25 patients included in Rainbowfish prompted FDA approval for treating infants younger than 2 months old as of May 2022.

The most common adverse events from these trials included rash, diarrhea, and aphthous ulcers. The FDA approval covers all SMA types and ages. Data on safety during pregnancy are insufficient as risdiplam does cross the placenta. Preclinical studies suggest potential teratogenicity. Data on lactation are also insufficient, although preclinical studies show transmission in breast milk. There is also a potential effect on spermatogenesis, supported exclusively by preclinical studies.

Combination Survival Motor Neuron–Directed Treatments

Although several trials are underway exploring the safety of any of these three treatments in participants previously exposed to another treatment, there is currently no evidence of efficacy for combining therapies aimed at increasing SMN protein production. The additional cost, the burden for the patients, and additional risk of adverse effects should be considered in parallel with the current absence of evidence of additional benefit from combined therapies. Several industry-sponsored clinical trials are ongoing to evaluate the safety and the potential additional benefit of nusinersen, risdiplam, or onasemnogene abeparvovec in patients previously treated with another disease-modifying treatment. Only safety data have so far been presented.

A shared informed decision-making process is encouraged when choosing which SMN-directed therapy to initiate or change to, based on available evidence by phenotype and age, preferred route of administration by the patient and family, available long-term outcome data on efficacy and adverse events, and availability based on local regulatory approval label and individual reimbursement criteria. For instance, the FDA label for onasemnogene abeparvovec includes only patients younger than 2 years old. In several countries, disease-modifying treatments are not funded for patients on permanent ventilation.

Non–Survival Motor Neuron–Directed Treatments

Although three drugs have gathered regulatory approval, significant unmet need remains, especially in the population of patients treated after symptom onset.[72] This has prompted the development of several therapies not dependent on increasing functional SMN as complementary targets.[73] The most advanced drug development pathway of this kind targets the myostatin pathways, as three drugs are currently in development (MANATEE,[63] RESILIENT,[74] and SAPPHIRE[75]). The strategy relies on inhibiting an inhibition pathway of muscle mass development (ie, increasing muscle mass) in patients already treated with disease-modifying treatment.

The second approach consists of facilitating neuromuscular junction transmission through acetylcholine esterase inhibitors[76] or presynaptic blockage of potassium channels by amifampridine.[77] To a certain extent, salbutamol, a

broadly off-label β_2-adrenoreceptor agonist drug, could act similarly, in addition to possible increased SMN protein expression.[78]

Finally, several drugs are considered to have the potential to increase SMN protein levels. Anti-inflammatory cyclooxygenase-2 inhibitors such as celecoxib activate the p38 pathway, which is involved in regulating *SMN* transcript stability. Moxifloxacin inhibits the activity of the enzyme topoisomerase II and affects the splicing of *SMN2*. Securinine promotes *SMN2* exon 7 inclusion and increases full-length *SMN2* mRNA and SMN protein. Rigosertib selectively modulates *SMN2* splicing and increases SMN protein levels. E1v1.11, a phosphorodiamidate morpholino oligomer is complementary to a region in the *SMN2* pre-mRNA and enhances exon 7 inclusion. Flunarizine increases SMN protein levels in the Cajal body, improves synaptic connection, and increases the survival of motor neurons. Finally, reldesemtiv, a small molecule that slows the rate of calcium release from the troponin complex of fast skeletal muscle fibers, has been studied in a recent double-blind placebo-controlled phase 2 trial.[79-81] Although the study did not demonstrate formal efficacy, a positive association was suggested at the higher dose on the 6-Minute-Walk Test.

CONCLUSION

Over the past decade, the care of individuals with SMA has completely changed with the availability of three disease-modifying therapies that increase SMN protein production. With demonstrated efficacy in improving survival and motor function in both the short and long term, earlier treatment is essential for the highest impact. Effectiveness of these therapies across a broader range of individuals remains uncertain, and additional real-world evidence is needed to address the long-term safety and effectiveness of these therapies. All treatments remain disease modifying, and none are curative. Vigilance is needed to observe the new natural history of disease impacting not only new motor phenotypes, including bulbar function and musculoskeletal comorbidities, but also across other developmental domains, especially in individuals with two copies of *SMN2*. Patient-centered outcome measures capturing endurance, real-world activity, and participation are needed to generate continued real-world observational data that can meaningfully impact care decisions. Inequity worldwide in access to standard of care such as wheelchairs and adaptive equipment, and ventilatory and nutritional support are only compounded by the unequal access to these disease-modifying therapies. Optimized supportive care remains essential, and vigilance is needed to define the new natural history of this disease.

USEFUL WEBSITES

BEFORE SMA
This website includes resources for health care professionals who treat patients with spinal muscular atrophy identified by newborn screening.
www.beforesma.com

CURE SMA
This patient organization website includes resources for patients, clinicians, and researchers, with toolkits to facilitate trial readiness as well as other resources and information.
www.curesma.org

VIDEO LEGENDS

VIDEO 12-1
Examination of a 4-year-old boy with spinal muscular atrophy type 3 and four copies of *SMN2*. Video shows the examination of the 4-year-old boy in CASE 12-1 who presents with symptoms of frequent falls and difficulty climbing stairs. All muscle stretch reflexes are present except at the knees. Gowers sign is present. Proximal muscle weakness is observed as the boy is asked to climb up on the bed. Genetic testing confirmed the homozygous absence of *SMN1* gene exon 7 and presence of four copies of the *SMN2* gene.

Modified with permission from Oskoui M, et al.[22] © 2020 American Academy of Neurology.

VIDEO 12-2
A 10-year-old boy with spinal muscular atrophy type 3 and four copies of *SMN2* showing a waddling gait. Video shows the boy in CASE 12-1 with spinal muscular atrophy type 3 at 10 years old. He has been treated with nusinersen since he was 2 years old, and he walks independently with a waddling gait.

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VIDEO 12-3
A 41-day-old presymptomatic infant boy with spinal muscular atrophy and two copies of *SMN2*. Video shows the 41-day-old boy in CASE 12-2 who was diagnosed with spinal muscular atrophy through newborn screening at 22 days old and treated with onasemnogene abeparvovec at 43 days old. Examination shows mild clinical signs in the lower limbs with reduced spontaneous antigravity movements and diminished but preserved reflexes.

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VIDEO 12-4
An 11-month-old boy with spinal muscular atrophy walking independently. Video demonstrates the boy in CASE 12-2 walking independently at 11 months old. He was diagnosed with spinal muscular atrophy through newborn screening at 22 days old and treated with onasemnogene abeparvovec at 43 days old.

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VIDEO 12-5
A 3-year-old boy with spinal muscular atrophy who can walk independently but has proximal motor weakness. Video demonstrates the boy in CASE 12-2 at 3 years old; he can walk independently but proximal motor weakness can be seen. He was diagnosed through newborn screening at 22 days old and treated with onasemnogene abeparvovec at 43 days old.

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VIDEO 12-6
A 26-year-old woman with spinal muscular atrophy type 2 on risdiplam treatment. Video shows the 26-year-old woman with spinal muscular atrophy type 2 in CASE 12-3 after 1 year of risdiplam treatment drinking tea, writing, typing, putting together blocks, and doing needlepoint. The risdiplam treatment aimed to improve distal limb function that impacted her daily activities. After 1 year of treatment, she can drink from a cup with a higher volume of tea, write and type for longer periods, and do manual tasks. She has three copies of the *SMN2* gene and was diagnosed at the age of 8 months.

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Multidisciplinary Clinics in Neuromuscular Medicine

By Kelly Gwathmey, MD; Terry D. Heiman-Patterson, MD

SELECTED TOPICS IN NEUROLOGY PRACTICE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

Multidisciplinary care is comprehensive, coordinated clinical care across medical disciplines and allied health professions. Neuromuscular disorders, such as amyotrophic lateral sclerosis and muscular dystrophies, are often associated with disabling weakness and extramuscular symptoms and may benefit from care in a model that consolidates numerous clinic visits into a single more efficient multidisciplinary clinic visit. The goal of the neuromuscular multidisciplinary care model is to improve patient outcomes, patient satisfaction, quality of life, access to medications and equipment, and survival. Although the costs of running a multidisciplinary clinic are high, they are likely associated with cost savings from the patient's perspective. Several barriers to acceptance of multidisciplinary clinics include the distance needed to travel to the clinic and the duration of the clinic visit. Telehealth multidisciplinary clinic visits may address some of these concerns. Further study is needed to understand the value of multidisciplinary clinics and is a necessary step toward creating a sustainable model.

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Address correspondence to Dr Kelly Gwathmey, 11958 W Broad St, Henrico, VA 23233, Kelly.Gwathmey@vcuhealth.org.

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INTRODUCTION

For many neuromuscular conditions, multidisciplinary care provides the most comprehensive, coordinated care across various medical disciplines and allied health professions, resulting in the best possible patient outcomes. In particular, patients who have neuromuscular disorders with severe disabling weakness and those who have disorders associated with extramuscular symptoms benefit from care in this setting. The “one-stop shopping” approach allows patients to be evaluated in a single visit by numerous specialists, including medical providers and ancillary therapists, reducing the burden of multiple appointments for patients with disabilities while also enabling health professionals to collaborate actively in developing care plans for complex diseases. Numerous professional societies, patient advocacy groups, and expert panels endorse this care model, and clinical practice guidelines recommend this care model for amyotrophic lateral sclerosis (ALS),[1] limb-girdle muscular dystrophy and distal muscular dystrophy,[2] spinal muscular atrophy,[3] and Duchenne muscular dystrophy specifically.[4]

In discussing this model of interprofessional care, it is important to recognize two types of care models: multidisciplinary and interdisciplinary. Although the neuromuscular literature primarily uses the term *multidisciplinary*, in reality,

most interprofessional neuromuscular clinics function in the interdisciplinary model. Across both care models, medical professionals caring for the patient complete evaluations in shared clinical spaces, whereas only in the interdisciplinary model is a formal meeting to discuss patient care among providers required.[5] Further, in interdisciplinary clinics, the treatment plan is formulated and coordinated by the entire team with the physician facilitating as an equal member of the team, rather than as a leader. Regardless of the interprofessional approach, the goals are the same: to be proactive rather than reactive in treatments and interventions and to provide preventive and longitudinal care over the course of the patient's lifetime. The term *multidisciplinary* is used in this article to be consistent with the literature published on this topic.

When considering the value of multidisciplinary clinics, one must weigh the patient outcomes relative to the costs of care delivery. The National Academy of Medicine developed a widely adopted definition of high-value health care as safe, timely, effective, efficient, equitable, and patient-centered, or *STEEEP* for short.[6] The Institute for Healthcare Improvement later created a framework to execute this approach, termed the *Triple Aim*, focusing on better patient outcomes, improved patient satisfaction, and lower costs.[7] Health care value is measured as the quality of care (outcomes, safety, and service) divided by the total cost of patient care over time. The neuromuscular multidisciplinary care model should provide improved patient outcomes, patient satisfaction, and resource utilization.[5] Furthermore, multidisciplinary care has been demonstrated to improve quality of life and survival across several neuromuscular diseases.[8-12]

The cost of running multidisciplinary clinics is high with the expense of sustaining this model often falling to the institution or supplemented by philanthropic funds and nonprofit clinical care grants.[13] One survey of 18 certified US ALS clinics found the average cost of staffing a multidisciplinary team was only US $500 per person seen in clinic.[13] This calculation, however, did not account for the uncompensated indirect patient care time (eg, patient calls or messages, medication orders, prior authorizations). Another study found that institutions lose more than US $300 per visit for a patient with ALS.[14] In patients with ALS, faster referral to a multidisciplinary clinic has been associated with modest cost savings (€2072 [US $2280 as of July 10, 2023] per patient in a 2017 study of ALS clinics in Ireland).[15] In 2015, Gladman and Zinman[16] investigated the annual cost of ALS care per patient across 12 international health care systems. The annual cost ranged from US $13,667 in Denmark to US $69,475 in the United States. These estimates did not include out-of-pocket patient expenses. The per-patient total cost of care for patients with ALS surpasses other neurologic disorders such as stroke, dementia, and Parkinson disease.

Despite the many positives of multidisciplinary care, some barriers to acceptance and utilization remain. Travel to the clinic is the most commonly cited barrier, compounded by the challenges experienced by those patients with mobility limitations. In one study of patients with ALS, more than half lived more than 50 miles from a multidisciplinary clinic, and more than one-quarter lived more than 100 miles from the clinic.[17] In a survey of 15 patients with ALS, travel was the only barrier to accessing multidisciplinary care and was an issue for 87%.[18] One potential solution to this problem is the incorporation of telehealth, which is addressed later in this article. A second barrier to the acceptance of multidisciplinary care is the duration of the multidisciplinary clinic

visits. Because the visit length may surpass 3 hours in some cases, patients are often left fatigued after the visit.

MULTIDISCIPLINARY CARE MODELS

Multidisciplinary clinics in neuromuscular medicine may assume different forms depending on the patient's needs. Two examples of different multidisciplinary care models are discussed in this section with an adult multidisciplinary clinic example, ALS, followed by a pediatric multidisciplinary clinic example, Duchenne muscular dystrophy. The advantages of these well-established care models are also discussed.

Adult Amyotrophic Lateral Sclerosis Model

ALS is a rapidly progressive and fatal neurologic disease caused by to motor neuron degeneration leading to death within 2 to 5 years of symptom onset for more than 80% of patients. An estimated 15,000 to 30,000 people in the United States are living with ALS, with a prevalence between 5.5 and 9.9 per 100,000.[19] The lifetime risk for developing ALS has been estimated to be 1 in 350 for men and 1 in 420 for women.[20] The disease is characterized by relentlessly progressive extremity weakness and weakness of respiratory and bulbar muscles. Apart from weakness, dyspnea, dysarthria, and dysphagia, patients may experience sialorrhea, fatigue, sleep disturbance, cramps, spasticity, depression, anxiety, and cognitive dysfunction. For supportive care, patients often receive gastrostomy tube placement, ventilatory support, augmentative alternative communication, and mobility devices. Given the rapid decline in function and complexity of their supportive care, patients with ALS are best followed in a multidisciplinary clinic.

Numerous disciplines are variably represented in this care model, including a physician (often a neurologist), social worker or case manager, physical therapist, occupational therapist, speech-language pathologist, respiratory therapist or pulmonologist, dietitian, genetic counselor or geneticist, and palliative care physician. A dedicated specialized nurse coordinator, in a liaison role, is also extremely beneficial. Voluntary support services in the form of national and regional patient advocacy associations are often present and involved in the multidisciplinary care model. These visits are lengthy; 90% last more than 3 hours according to a recent survey of ALS centers across the Northeast Amyotrophic Lateral Sclerosis Consortium. Patients are usually seen every 2 to 3 months in the multidisciplinary clinic with regular contact with patients and caregivers between visits.[21]

To highlight the value of the multidisciplinary care model in ALS, the American Academy of Neurology (AAN) developed quality measures to address gaps in patient care, overcome the underutilization of evidence-based therapeutics for individuals with ALS, and help clinicians measure and improve the quality of care for these patients.[22] These AAN ALS quality measures, which use a patient-centered approach to proactive decision making, emphasize supportive care and planning for complex care needs. These measures encourage the use of a multidisciplinary model, including treatment of respiratory and nutritional dysfunction, treatment of disease-related symptoms, treatment of functional changes, prescribing of disease-modifying agents, and support for the eventual transition to hospice care. Similar clinical management guidelines for ALS exist in Europe.[23] Multidisciplinary care is required to deliver the

highest-quality care to patients with ALS through harmonious collaboration, coordination, and transition among numerous health care professionals across a range of health care services and disciplines.[21]

The value of multidisciplinary care for patients with ALS is well defined. Patients who are followed in these clinics have longer survival,[24-27] fewer hospitalizations,[9,28] better quality of life,[10] and greater access to therapies for ALS.[9,10,29] A 2021 meta-analysis of six studies demonstrated a mean survival advantage of 141.67 days for patients followed in a multidisciplinary clinic compared with non–multidisciplinary care.[26] Additionally, multidisciplinary care improves the outcomes for patients with ALS independent of ventilatory use, gastrostomy tube use, and riluzole use.[30]

Patients with ALS and their caregivers also report positive experiences with the multidisciplinary clinic. One survey study reported an improved sense of efficiency and greater collaboration with the team.[31] One study highlighted that access to integrated care and research opportunities were aspects of the multidisciplinary care model that patients with ALS value.[32]

Pediatric Duchenne Muscular Dystrophy Model

Duchenne muscular dystrophy is a progressive disorder resulting from variations in the dystrophin gene located on the X chromosome. It is estimated to affect 15.9 to 19.5 per 100,000 newborn boys.[33] Because it is a terminal illness, the focus of clinical care is symptomatic management and improvement of quality of life.[34] Over time, patients experience a progressive decline in mobility resulting in wheelchair use, cardiac involvement, and respiratory failure necessitating noninvasive and occasionally invasive ventilation. Ultimately, patients die from cardiac or respiratory complications.

The US Congress authorized the Muscular Dystrophy Community Assistance, Research and Education Amendments (MD CARE Act) in 2001 and subsequently reauthorized the Act in 2008.[4,35-38] In response to this, the Centers for Disease Control and Prevention and the National Center on Birth Defects and Developmental Disabilities gathered with Duchenne muscular dystrophy experts to develop standard guidelines for Duchenne muscular dystrophy care with the goal of improving health outcomes. These recommendations were intended "to provide a framework for recognising the primary manifestations and possible complications and for planning optimum treatment across different specialties with a coordinated multidisciplinary team" and were ultimately published as the Care Considerations in 2010 (FIGURE 1).[35,36]

Similar to ALS, patient advocacy organizations, such as Parent Project Muscular Dystrophy (PPMD) and the Muscular Dystrophy Association, have developed models of center-based comprehensive multidisciplinary Duchenne muscular dystrophy care.[39] The five primary domains necessary for the provision of high-level care in Duchenne muscular dystrophy, aligned with the Care Considerations, include neuromuscular (neurology, physical medicine and rehabilitation, and physical and occupational therapy), cardiac, pulmonary, and endocrine and bone health, as well as coordination and communication. The PPMD Duchenne Care Center Standards of Certification lists the program requirements for care and services including the following providers available at each visit: center director, clinic coordinator (nurse or nurse practitioner), neurologist or physical medicine and rehabilitation specialist with expertise in

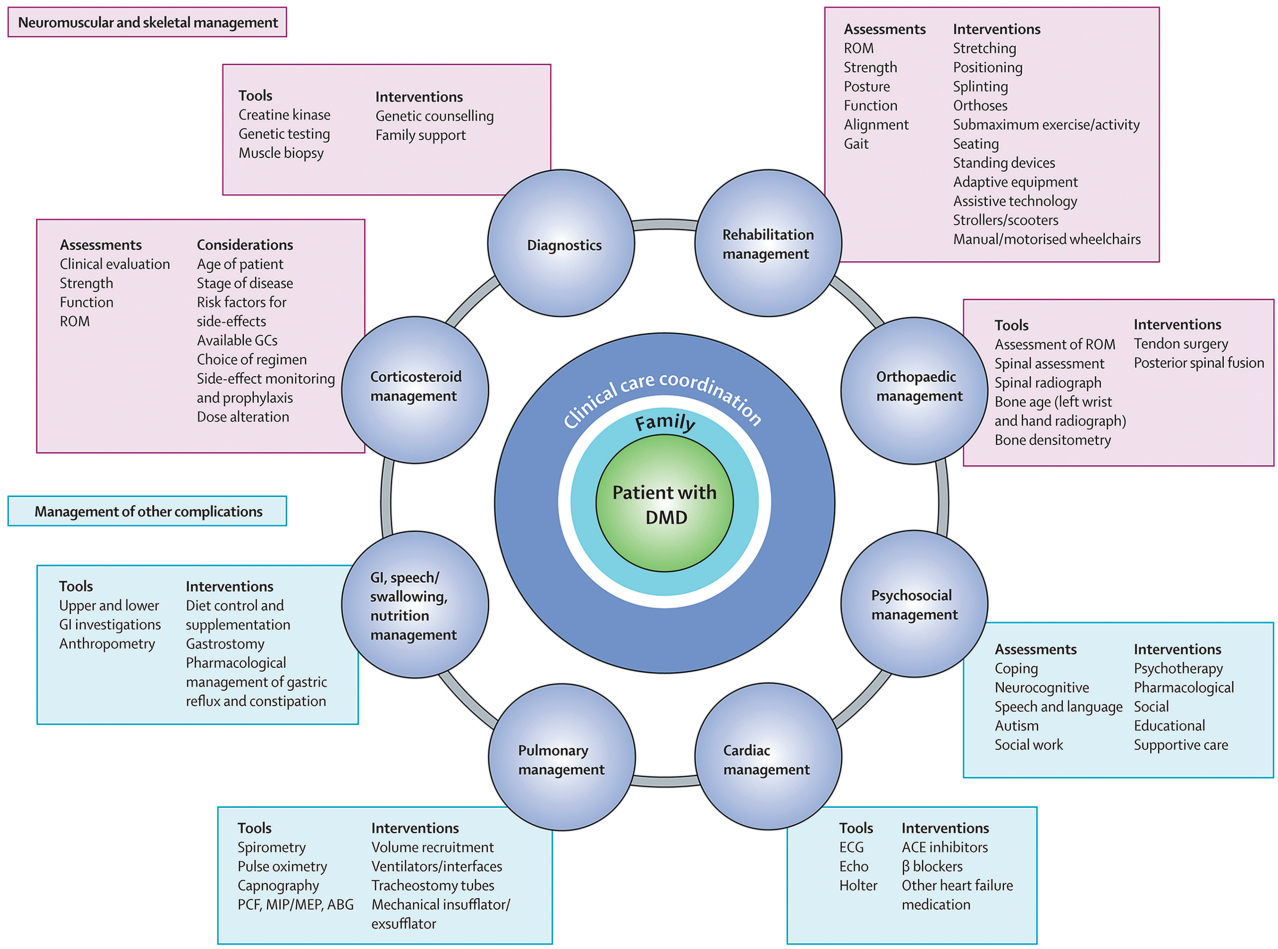

FIGURE 1

Interdisciplinary care of patients with Duchenne muscular dystrophy (DMD) is a crucial component of the management of DMD. This care is best provided in a multidisciplinary care setting in which the individual and family can access expertise for the required multisystem management of DMD in a collaborative effort.

ABG = arterial blood gas; ACE = angiotensinconverting enzyme; Echo = echocardiogram; ECG = electrocardiogram; GC = glucocorticoids; GI = gastrointestinal; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PCF = peak cough flow; ROM = range of motion. Reprinted with permission from Bushby K, et al, Lancet.[36] © 2010 Elsevier Ltd.

neuromuscular medicine, cardiologist, pulmonologist, genetic counselor, physical therapist, and social worker. Numerous other subspecialists and clinical services must be available on an as-needed basis, including orthopedics, endocrinology, gastroenterology, urology, palliative care, surgery, durable medical equipment vending, orthotics, occupational therapy, wheelchair consultation, nutrition, speech therapy, and cognitive-behavioral health (psychologist or neuropsychologist, counselor, developmental pediatrician). With the implementation of the PPMD Certified Duchenne Care Center Program, children with non–Duchenne muscular dystrophy neuromuscular disorders have also benefited from this robust multidisciplinary care model.

Among the benefits of care within a Duchenne muscular dystrophy–focused multidisciplinary clinic is an increase in survival.[40] In combination with better

ventilatory support, multidisciplinary clinic care has been credited with improving life expectancy for these patients into their thirties.[41]

In 2022, the estimated cost associated with being treated according to the Duchenne muscular dystrophy Care Considerations is a 20-year per-patient cumulative cost of $174,701 if treated with prednisone versus US $2.3 million if treated with deflazacort. The estimated out-of-pocket expense for this care is US $12,643 for prednisone versus US $29,194 for deflazacort.[42]

Several specific factors should be considered in the delivery of pediatric neuromuscular multidisciplinary care. Key requirements in this patient population are coordination and communication with the patient's general pediatrician. This is of utmost importance, especially if the patient lives a considerable distance from the clinic.[14] Also, these patients greatly benefit from the presence of a transition-of-care team or transitional clinic for young adult patients moving to adult multidisciplinary care.[43]

ADDITIONAL CONSIDERATIONS

The advent of both telemedicine clinic visits and accessible genetic testing has improved patient access to multidisciplinary care and diagnostic yield. These topics represent significant advances in the delivery of neuromuscular multidisciplinary care.

Telehealth

Telehealth visits, especially in ALS multidisciplinary clinics, have long been utilized to reduce the travel burden and curtail the length of the clinic visit. These telehealth visits may replace routine in-person visits, supplement in-person visits, and replace urgent in-person visits. More recently, the COVID-19 pandemic ushered in telehealth visits as a mainstream means to deliver health care, and, unlike in the past, providers are more likely to receive reimbursement for these rendered services. Numerous studies have reported the benefits of telemedicine in ALS.[44–52] One study conducted in the Cleveland VA ALS Center found that patients followed via telemedicine visits achieved the same AAN quality measures performance as those followed in person.[49] The standard telemedicine approach is to have the ALS clinic team use a live videoconference to communicate with patients in their homes or a health care facility and is the synchronous visit model. In addition to the standard synchronous telemedicine approach, the asynchronous "store and forward" method has been demonstrated to be effective.[52] This telehealth model involves patients evaluated in their homes by trained providers. This recorded evaluation is later reviewed by the multidisciplinary team, and the recommendations are communicated to the patient. Patients seen in this care model reported higher satisfaction ratings compared with standard clinic visits.

The adoption of the telehealth model in a multidisciplinary clinic presents understandable challenges and barriers. First, the examination of the patient is quite limited when completed with video teleconference. Specific to ALS, important data, such as weight and vital capacity, are often unavailable remotely, which limits physicians' ability to determine when noninvasive ventilation and gastrostomy tube placement should be pursued. Also, in the synchronous model, all ALS team members must be present simultaneously to conduct the visit. Currently, asynchronous visits are generally not reimbursed at the same level as synchronous care, and regardless of the type of telemedicine visit, patients must have access to the internet and technology necessary to launch a video visit.

Genetic Testing

In both adult and pediatric multidisciplinary clinics, incorporating genetic counselors, neurogeneticists, and genetic testing has never been more important. For pediatric and adult patients with neuromuscular disorders, recognition of disease-causing variations is now facilitated by the wide availability of free genetic testing for most inherited neuromuscular disorders. Not only has the advent of genetic testing supplanted the need for invasive diagnostic testing, such as electrophysiologic studies and tissue biopsy in some cases, but it also opens the door to novel, targeted genotype-specific treatments exemplified by the recent FDA approval of toferson for the treatment of patients with *SOD1*-associated ALS. Genetic counselors and geneticists additionally have an important role in interpreting and counseling regarding variants of uncertain significance that are commonly encountered on next-generation sequencing panels; they can also counsel and potentially test asymptomatic at-risk family members.

FUTURE DIRECTIONS

There are clear benefits in quality of care, quality of life, and survival for patients with progressive neuromuscular disease followed in a comprehensive, coordinated multidisciplinary clinic model. However, the sustainability of the multidisciplinary clinic model is threatened because the value of this care model is difficult to quantify.[14] The multidisciplinary model is costly to implement and execute. In a recent survey of directors of 61 ALS multidisciplinary clinics, 92% of centers relied on philanthropy and 59% on their institutions for financial support. One-third of the clinic directors also utilized other sources.[53] Only 25% of clinics were able to support themselves through various sources of philanthropy along with separate billing for each discipline. Understanding the true cost of running a neuromuscular multidisciplinary clinic is a priority for future research, and an extensive survey study of ALS multidisciplinary clinics to answer this question is currently ongoing.

In addition to the financial cost of maintaining multidisciplinary clinics, the emotional toll that this clinical model and care of chronically ill and terminally ill patients takes on the providers must be considered. In a survey of ALS care providers and clinic managers, a high level of stress was reported, and in some, stress and operational issues were significant enough that these providers and managers considered leaving their positions.[54] The sources of stress include the delivery of the diagnosis of a terminal disease and its prognosis, changing goals of care to comfort only, and frequently encountered ethical dilemmas in the treatment or transition from survival-prolonging care. Health care organizations must ensure health professionals in multidisciplinary clinics are both financially and emotionally supported in their role as service providers.[21,55]

An improved understanding of the value that the multidisciplinary clinic care model provides is a necessary step toward creating a sustainable model. Across ALS, Duchenne muscular dystrophy, and other neuromuscular conditions followed in the multidisciplinary clinics, an appreciation of how care in these clinics affects health care utilization is imperative. This poorly understood outcome should be a research priority in the future. Demonstrating that multidisciplinary clinic care results in less health care utilization and improved quality of life, quality of care, and survival may convey to payers the true value of the multidisciplinary clinic model. Currently, many multidisciplinary clinics

submit only a single physician charge for the lengthy multidisciplinary clinic visit to eliminate the need for patients to pay multiple copayments at a single time. Coding and billing for same-day collaborative care with both a physician and nonphysician are complicated, and the potential charges are not easy to manage. Hopefully, with time, neuromuscular disease stakeholders, including providers, patients, caregivers, and patient advocacy organizations, can advocate for improved reimbursement for this care model to support and sustain multidisciplinary clinics without reliance on philanthropic funds, organizational support, and volunteerism.

CONCLUSION

The multidisciplinary care model provides benefits to patients with neuromuscular conditions including high-quality clinical care, improved quality of life, and prolonged survival. Although it is the consensus best care model for diseases such as ALS and Duchenne muscular dystrophy, the sustainability of this model is threatened by the high cost of implementation and the emotional toll it takes on clinic providers. Further study exploring the impact of multidisciplinary care on health care utilization is necessary to assure policymakers and payers of this model's value.

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PERIPHERAL NERVE AND MOTOR NEURON DISORDERS

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1	A	B	C	D	E	21	A	B	C	D	E
2	A	B	C	D	E	22	A	B	C	D	E
3	A	B	C	D	E	23	A	B	C	D	E
4	A	B	C	D	E	24	A	B	C	D	E
5	A	B	C	D	E	25	A	B	C	D	E
6	A	B	C	D	E	26	A	B	C	D	E
7	A	B	C	D	E	27	A	B	C	D	E
8	A	B	C	D	E	28	A	B	C	D	E
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16	A	B	C	D	E	36	A	B	C	D	E
17	A	B	C	D	E	37	A	B	C	D	E
18	A	B	C	D	E	38	A	B	C	D	E
19	A	B	C	D	E	39	A	B	C	D	E
20	A	B	C	D	E	40	A	B	C	D	E

Postreading Self-Assessment and CME Test

By Douglas J. Gelb, MD, PhD, FAAN; Nuri Jacoby, MD, FAAN

PERIPHERAL NERVE AND MOTOR NEURON DISORDERS

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ARTICLE 1: LOCALIZATION AND DIAGNOSTIC EVALUATION OF PERIPHERAL NERVE DISORDERS

1 Which of the following symptoms is most suggestive of a genetic neuropathy?

A early satiety
B lack of paresthesia
C multifocal anatomic distribution
D significant weakness in the legs
E subacute onset

2 Which of the following disorders that cause a peripheral neuropathy is most likely to have abnormal heart rate variability?

A amyloidosis
B chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
C cyanocobalamin deficiency
D human immunodeficiency virus (HIV)
E Sjögren syndrome

3 When evaluating a patient with symptoms and signs consistent with a distal symmetric polyneuropathy, which of the following serum laboratory tests is considered the highest yield?

A erythrocyte sedimentation rate
B human immunodeficiency virus (HIV) antigen
C Lyme antibody
D rheumatoid factor
E serum electrophoresis with immunofixation

ARTICLE 2: GUILLAIN-BARRÉ SYNDROME

4 Which of the following types of arrhythmia is most common in people with Guillain-Barré syndrome?

A atrial fibrillation
B long QT syndrome
C second-degree atrioventricular block
D sinus tachycardia
E third-degree atrioventricular block

5 **Which of the following features is more typical of acute motor axonal neuropathy (AMAN) than of acute motor and sensory axonal neuropathy (AMSAN)?**

A antecedent respiratory infection
B autonomic dysfunction
C cranial nerve dysfunction
D intact muscle stretch reflexes
E severe residual disability

6 **Miller Fisher syndrome is most commonly associated with antibodies to which of the following gangliosides?**

A Gal-C
B GalNac-GD1a
C GM1
D GM2
E GQ1b

7 **In a patient with a clinical syndrome suggestive of Guillain-Barré syndrome, which of the following cerebrospinal fluid results should prompt evaluation for alternative diagnoses?**

A glucose of 70 mg/dL
B opening pressure of 25 cm H_2O
C protein of 70 mg/dL
D red blood cell count of 110 cells/mm^3
E white blood cell count of 80 cells/mm^3

ARTICLE 3: CHRONIC IMMUNE-MEDIATED DEMYELINATING NEUROPATHIES

8 **A 72-year-old man with a past medical history of nonischemic cardiomyopathy and congestive heart failure presents for follow-up for a severe subacute length-dependent neuropathy. He has weakness, numbness, severe burning pain in bilateral distal arms and legs, areflexia, and orthostatic hypotension. Electrodiagnostic studies demonstrate slowing of conduction velocities and prolonged distal latencies, and laboratory values including serum immunofixation electrophoresis and hemoglobin A_{1C} are normal. A tentative diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy is made. He undergoes an initial treatment course with a loading dose and two maintenance doses every 3 weeks of IV immunoglobulin (IVIg), but his clinical symptoms continue to worsen. What is the next best step in management?**

A bone marrow biopsy
B genetic testing
C IV steroids

D nerve biopsy
E rituximab

9 Which of the following signs or symptoms is more consistent with a diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome rather than chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)?

A asymmetric weakness
B better response to steroids
C presence of tremor
D prominent pain
E weakness more prominent than numbness

10 Which of the following medications can cause a demyelinating neuropathy that clinically appears similar to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)?

A infliximab (tumor necrosis factor α antagonist)
B isoniazid
C metronidazole
D nitrofurantoin
E paclitaxel

ARTICLE 4: AUTOIMMUNE AXONAL NEUROPATHIES

11 Which of the following diagnoses is most likely in a patient with mononeuropathy multiplex, asthma, and positive perinuclear antineutrophil cytoplasmic autoantibody (ANCA) serology?

A eosinophilic granulomatosis with polyangiitis
B granulomatosis with polyangiitis
C microscopic polyangiitis
D polyarteritis nodosa
E sarcoidosis

12 In patients who have mononeuritis multiplex due to granulomatosis with polyangiitis, which of the following medications should be used in conjunction with corticosteroids to induce remission of the granulomatosis with polyangiitis?

A azathioprine
B cyclophosphamide
C cyclosporine
D mycophenolate
E rituximab

13 **Two days after a hysterectomy for endometriosis, a 31-year-old woman develops severe pain and weakness in the proximal right lower extremity. She has no medical conditions other than the endometriosis. Examination reveals prominent weakness of right hip flexion and knee extension, with mild weakness of knee flexion and ankle dorsiflexion. The right patellar reflex is absent. Complete blood cell count, comprehensive metabolic profile, and glycosylated hemoglobin level are all normal. Which of the following conditions is most likely?**

A diabetic lumbosacral radiculoplexus neuropathy
B mononeuritis multiplex
C postsurgical inflammatory neuropathy
D retroperitoneal hematoma
E traction injury of L4 nerve root

14 **Which of the following underlying malignancies is most likely in a patient who has a sensory neuronopathy and antineuronal nuclear antibody 1 (ANNA-1)?**

A ovarian cancer
B prostate cancer
C seminoma
D small cell lung cancer
E thymoma

ARTICLE 5: DIABETIC NEUROPATHIES

15 **A 92-year-old man with type 2 diabetes and anxiety presents for follow-up for management of neuropathic pain in his feet. He is on duloxetine 60 mg daily, which he says has decreased his pain from 9 to 6 out of 10. Despite the improvement, he feels the pain continues to affect his sleep and quality of life. What is the next best step in management?**

A add amitriptyline to the current regimen
B add gabapentin to the current regimen
C refer for consideration of a spinal cord stimulator
D stop duloxetine and add amitriptyline
E stop duloxetine and add gabapentin

16 **Which of the following is one of the earliest manifestations of cardiovascular autonomic neuropathy?**

A abnormal blood pressure
B decreased exercise tolerance
C dizziness
D elevated resting heart rate
E erectile dysfunction

17 **What is the approximate absolute risk of developing treatment-induced neuropathy of diabetes in a patient with type 2 diabetes whose hemoglobin A_{1c} decreases by 4.5% in 3 months after initiation of insulin?**

- A 20%
- B 40%
- C 60%
- D 80%
- E 100%

ARTICLE 6: INFECTIOUS NEUROPATHIES

18 **A skin eruption on the tip or side of the nose in someone with herpes zoster is associated with an 80% likelihood of developing which of the following conditions?**

- A ocular involvement
- B postherpetic neuralgia
- C Ramsay Hunt syndrome
- D recurrent episodes of herpes zoster in the trigeminal distribution
- E widely disseminated herpes zoster

19 **A patient with human immunodeficiency virus (HIV) infection has urinary retention, constipation, and bilateral lower extremity weakness that started 1 week ago and has progressed rapidly. The patient does not have a rash. Examination reveals normal mental status, cranial nerves, and upper extremity function, with severe weakness, sensory loss, and areflexia in both lower extremities. CSF is notable for neutrophilic leukocytosis. Which of the following infections is most likely?**

- A central nervous system lymphoma
- B *Cryptococcus*
- C cytomegalovirus
- D herpes simplex virus
- E herpes zoster virus

20 **Tender, beaded, thickened nerves are characteristic of neuropathy due to which of the following infections?**

- A cytomegalovirus
- B hepatitis C
- C human immunodeficiency virus (HIV)
- D *Mycobacterium leprae*
- E severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

21 Which of the following types of peripheral nervous system disorder is most common in patients with human immunodeficiency virus (HIV) infection?

A acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
B chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
C distal symmetric polyneuropathy
D facial nerve palsy
E mononeuropathy multiplex

ARTICLE 7: TOXIC NEUROPATHIES

22 A 46-year-old man with testicular cancer presents to the office for numbness in his hands and feet for the past 4 months. The symptoms began while he was on chemotherapy. The patient's oncologist then stopped it 2 months ago, but despite stopping chemotherapy, the symptoms have worsened. On examination, the patient has stocking-glove loss to light touch and pinprick and has decreased vibration sensation and joint position. Motor strength is normal. Laboratory test results have not revealed another cause of the neuropathy. Which of the following is the most likely chemotherapy that caused this patient's symptoms?

A bortezomib
B cisplatin
C docetaxel
D lenalidomide
E vincristine

23 Which medication is recommended as first-line therapy by the American Society of Clinical Oncology for the treatment of neuropathic pain due to chemotherapy-induced peripheral neuropathy?

A amitriptyline
B duloxetine
C gabapentin
D mexiletine
E pregabalin

ARTICLE 8: NUTRITIONAL NEUROPATHIES

24 Sensory neuronopathy can result from excessive intake of which of the following vitamins?

A B_1 (thiamine)
B B_2 (riboflavin)

C B_3 (niacin)
D B_6 (pyridoxine)
E B_9 (folate)

25 Nitrous oxide toxicity results in the same symptoms and signs as a deficiency of which of the following vitamins?

A B_1 (thiamine)
B B_2 (riboflavin)
C B_3 (niacin)
D B_6 (pyridoxine)
E B_{12} (cobalamin)

26 Which of the following tests is most specific for pernicious anemia?

A anti-intrinsic factor antibodies
B antiparietal cell antibodies
C homocysteine
D mean corpuscular volume
E pepsinogen

27 Deficiency of which of the following vitamins is most likely to cause a rapidly progressive peripheral polyneuropathy that mimics Guillain-Barré syndrome?

A B_1 (thiamine)
B B_2 (riboflavin)
C B_6 (pyridoxine)
D B_9 (folate)
E B_{12} (cobalamin)

ARTICLE 9: PARAPROTEINEMIC NEUROPATHIES

28 An 82-year-old man presents with 9 months of unsteady gait and numbness in his feet. The unsteady gait is markedly worse at night. He denies significant weakness, neck pain, or bowel and bladder symptoms. Examination is notable for a stocking distribution to pinprick, decreased vibration sensation and joint position sense in the lower extremities, action tremors of both hands, diffusely reduced reflexes, and a positive Romberg sign. Laboratory values are significant for an IgM monoclonal gammopathy. Which of the following electrodiagnostic findings of the motor nerves would be most likely in this patient?

A conduction block
B normal motor nerves

C severely decreased compound muscle action potential (CMAP) amplitudes
D severely prolonged distal latencies
E uniform severely reduced conduction velocities

29 **Which of the following paraproteinemic subtypes is most associated with a neuropathy?**

A IgA
B IgD
C IgE
D IgG
E IgM

30 **A 52-year-old man presents to the office with 18 months of progressively worsening unsteady gait and diplopia. He now requires the use of a walker, and he cannot feel the ground when he walks. On examination, the patient has ophthalmoplegia, intact motor strength, stocking-glove sensory loss with severely impaired vibration sensation and joint position sense in his toes, and areflexia. Neuropathy laboratory values are significant for an IgM monoclonal gammopathy. Electrodiagnostic studies are consistent with an acquired demyelinating polyneuropathy. The patient previously was treated for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with a 6-month trial of IV immunoglobulin (IVIg) without any benefit. Which of the following is the most appropriate treatment for this patient?**

A hematopoietic cell transplantation
B lenalidomide
C plasma exchange
D prednisone
E rituximab

ARTICLE 10: HEREDITARY NEUROPATHIES

31 **Nerve conduction studies showing prolonged distal motor latencies and conduction block at compressible sites are characteristic of which of the following hereditary neuropathies?**

A Charcot-Marie-Tooth disease type 1A (CMT1A)
B CMT1B
C CMT1X
D CMT2A
E hereditary neuropathy with liability to pressure palsies (HNPP)

32 **A teenager who has severe skin ulcerations in the feet, absent pain sensation from the knees down, anhidrosis, and gastrointestinal dysmotility most likely has a variation in a gene coding for a subunit of which of the following proteins?**

A connexin 32
B mitofusin 2
C peripheral myelin protein 22
D serine palmitoyltransferase
E sorbitol dehydrogenase

ARTICLE 11: AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

33 **Which of the following clinical features are more commonly seen in patients with primary lateral sclerosis rather than hereditary spastic paraplegia?**

A bladder dysfunction
B gradual progression of symptoms
C orthostatic hypotension
D paresthesia
E spastic dysarthria

34 **A 63-year-old woman with a past medical history of hypertension and diabetes presents for evaluation of unsteady gait. The patient has had several falls in the past 6 months and says that her right leg is giving out on her. It is harder for her to lift heavy objects and more difficult to use her hands. Her partner has also noticed the patient is less empathetic with friends and family and that she predominantly wants to eat dessert and as a result has recently gained 9 kg (20 lb). On mental status examination, she scores 18 of 30 on the Montreal Cognitive Assessment with deficits most pronounced in executive function. Motor examination reveals atrophy, weakness, and hyperreflexia in both arms and her right leg. Which genetic variation is the most likely cause of the patient's clinical presentation?**

A *ALS2*
B *C9orf72*
C *FUS*
D *SOD1*
E *TARDBP*

35 **Which of the following blood tests must be monitored when starting a patient on riluzole?**

- A creatinine
- B liver function
- C platelet count
- D sodium
- E white blood cell count

36 **A 74-year-old man with amyotrophic lateral sclerosis presents for follow-up. His weakness has mildly worsened since his last visit. He occasionally chokes on his saliva and when eating although he does not feel it has worsened since the last visit and he has not noticed excessive salivation. He does not report having orthopnea, morning headaches, or shortness of breath. He is on riluzole and edaravone. Pulmonary function tests demonstrate a forced vital capacity of 80%, maximum inspiratory pressure of -70 cm H_2O, and a cough peak flow of 250 L/min. Which of the following is the most appropriate next step in management?**

- A invasive mechanical ventilation
- B mechanical insufflation-exsufflation
- C noninvasive ventilation
- D placement of gastrostomy tube
- E sublingual atropine

ARTICLE 12: SPINAL MUSCULAR ATROPHY

37 **Which of the following medications modulates the splicing of the *SMN2* pre-mRNA?**

- A amifampridine
- B nusinersen
- C onasemnogene abeparvovec
- D reldesemtiv
- E salbutamol

38 **Which of the following medications increases the production of full-length survival motor neuron (SMN) protein by introducing the *SMN1* gene copy?**

- A amifampridine
- B nusinersen
- C onasemnogene abeparvovec
- D reldesemtiv
- E risdiplam

39 **Which of the following medications is administered intrathecally?**

A celecoxib
B dalfampridine
C nusinersen
D risdiplam
E salbutamol

40 **Which of the following muscle stretch reflexes is typically the first to be lost as spinal muscular atrophy progresses?**

A biceps
B brachioradialis
C calcaneal
D patellar
E triceps

Postreading Self-Assessment and CME Test—Preferred Responses

By Douglas J. Gelb, MD, PhD, FAAN; Nuri Jacoby, MD, FAAN

PERIPHERAL NERVE AND MOTOR NEURON DISORDERS

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this Continuum issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

US PARTICIPANTS: Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at continpub.com/CME, participants may earn up to 20 AMA PRA Category 1 Credits™ toward SA-CME. US participants have up to 3 years from the date of publication online to earn SA-CME credits.

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ARTICLE 1: LOCALIZATION AND DIAGNOSTIC EVALUATION OF PERIPHERAL NERVE DISORDERS

1 The preferred response is **B (lack of paresthesia).** Genetic neuropathies tend to have an absence of positive sensory symptoms such as neuropathic pain, allodynia, dysesthesias, and paresthesia. For more information, refer to **page 1315** of the *Continuum* article "Localization and Diagnostic Evaluation of Peripheral Nerve Disorders."

2 The preferred response is **A (amyloidosis).** Amyloidosis, both hereditary and sporadic, often causes significant dysautonomia. Dysautonomia can be assessed by a tilt-table test, heart rate variability, quantitative sudomotor axon reflex testing, and thermoregulatory sweat testing. The other answer choices are not typically associated with abnormal autonomic function testing. For more information, refer to **page 1321** of the *Continuum* article "Localization and Diagnostic Evaluation of Peripheral Nerve Disorders."

3 The preferred response is **E (serum electrophoresis with immunofixation).** The American Academy of Neurology Practice Parameter from January 2009 states that fasting glucose, serum vitamin B_{12} with metabolites, and serum protein immunofixation electrophoresis are the highest yield in patients who present with a distal symmetric polyneuropathy. For more information, refer to **pages 1321** and **1323** of the *Continuum* article "Localization and Diagnostic Evaluation of Peripheral Nerve Disorders."

ARTICLE 2: GUILLAIN-BARRÉ SYNDROME

4 The preferred response is **D (sinus tachycardia).** Sustained sinus tachycardia is the most common cardiac arrhythmia in people with Guillain-Barré syndrome. For more information, refer to **pages 1332** to **1333** of the *Continuum* article "Guillain-Barré Syndrome."

5 The preferred response is **D (intact muscle stretch reflexes).** Muscle stretch reflexes may be normal or even increased in acute motor axonal neuropathy (AMAN). Acute motor and sensory axonal neuropathy (AMSAN) is often more severe than AMAN, and it is associated with severe residual disability. AMSAN is often associated with autonomic and cranial nerve dysfunction. AMSAN is typically preceded by respiratory infection, whereas AMAN is typically preceded by diarrheal illness. For more information, refer to **page 1333** of the *Continuum* article "Guillain-Barré Syndrome."

6 The preferred response is **E (GQ1b).** Approximately 85% to 90% of people with Miller Fisher syndrome have antibodies to the GQ1b ganglioside. For more information, refer to **page 1334** of the *Continuum* article "Guillain-Barré Syndrome."

7 The preferred response is **E (white blood cell count of 80 cells/mm^3).** Up to 5% of people with Guillain-Barré syndrome have mild cerebrospinal fluid pleocytosis, but the white blood cell count is usually 20 cells/mm^3 or less. A cerebrospinal fluid white blood cell count of more than 50 cells/mm^3 should prompt evaluation for other causes. Elevated cerebrospinal fluid protein is typical of Guillain-Barré syndrome, and elevated intracranial pressure can occur when the protein concentration is high enough. For more information, refer to **page 1341** of the *Continuum* article "Guillain-Barré Syndrome."

ARTICLE 3: CHRONIC IMMUNE-MEDIATED DEMYELINATING NEUROPATHIES

8 The preferred response is **B (genetic testing).** The patient's clinical history and lack of response to IV immunoglobulin (IVIg) should make the clinician question the initial diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The past medical history of nonischemic cardiomyopathy and congestive heart failure, the presence of significant neuropathic pain, and the dysautonomia are all atypical for CIDP and point to a possible diagnosis of hereditary transthyretin amyloidosis-related neuropathy. Therefore, genetic testing for a *TTR* variation would be the next most appropriate step. For more information, refer to **pages 1366** to **1367** of the *Continuum* article "Chronic Immune-Mediated Demyelinating Neuropathies."

9 The preferred response is **D (prominent pain).** POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome is a common mimic of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and should be considered when seeing a patient with a chronic demyelinating polyneuropathy. Prominent pain is more commonly seen in POEMS syndrome than in CIDP and, if present, should be a clue that CIDP may not be the diagnosis, particularly if diagnostic criteria for CIDP are not met or the patient has no response to first-line treatments for CIDP. For more information, refer to **page 1365** of the *Continuum* article "Chronic Immune-Mediated Demyelinating Neuropathies."

10 The preferred response is **A (infliximab).** Although all of the answer choices can cause a peripheral neuropathy, infliximab, a tumor necrosis factor α antagonist, is the sole choice from these options that can cause a demyelinating neuropathy. For more information, refer to **pages 1366** to **1367** of the *Continuum* article "Chronic Immune-Mediated Demyelinating Neuropathies."

ARTICLE 4: AUTOIMMUNE AXONAL NEUROPATHIES

11 The preferred response is **A (eosinophilic granulomatosis with polyangiitis).** Adult-onset asthma is present in up to 91% of patients with eosinophilic granulomatosis with polyangiitis, and myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody (ANCA) is the antibody most commonly associated with eosinophilic granulomatosis with polyangiitis. For more information, refer to **page 1386** of the *Continuum* article "Autoimmune Axonal Neuropathies."

12 The preferred response is **E (rituximab)**. Published guidelines from the American College of Rheumatology and the Vasculitis Foundation recommend using glucocorticoids and rituximab for induction of remission in patients with active severe granulomatosis with polyangiitis (GPA). Patients with GPA who have mononeuritis multiplex are classified as being in the severe category. For more information, refer to **pages 1383** to **1384** of the *Continuum* article "Autoimmune Axonal Neuropathies."

13 The preferred response is **C (postsurgical inflammatory neuropathy)**. This patient's clinical manifestations are typical of lumbosacral radiculoplexus neuropathy, which is the most common presentation of postsurgical inflammatory neuropathy. These clinical manifestations would also be typical of diabetic lumbosacral radiculoplexus neuropathy, but the onset 2 days after pelvic surgery in a patient with no history of diabetes and normal serum glucose and glycosylated hemoglobin levels makes postsurgical inflammatory neuropathy more likely. Retroperitoneal hematoma and injury of the L4 nerve root would not cause weakness of knee flexion or ankle dorsiflexion. For more information, refer to **page 1387** of the *Continuum* article "Autoimmune Axonal Neuropathies."

14 The preferred response is **D (small cell lung cancer)**. The most common underlying malignancy associated with antineuronal nuclear antibody 1 (ANNA-1) is small cell lung cancer. For more information, refer to **pages 1394** to **1395** of the *Continuum* article "Autoimmune Axonal Neuropathies."

ARTICLE 5: DIABETIC NEUROPATHIES

15 The preferred response is **B (add gabapentin to the current regimen).** The OPTION-DM (Optimal Pathway for Treating Neuropathic Pain in Diabetes Mellitus) trial showed that the addition of a second agent further improved pain control in patients with painful distal symmetric polyneuropathy. Therefore, the addition of a second medication for this patient is preferable to switching the duloxetine to another medication. Given the patient's age, gabapentin is preferable to amitriptyline. For more information, refer to **pages 1404** to **1405** of the *Continuum* article "Diabetic Neuropathies."

16 The preferred response is **D (elevated resting heart rate).** Cardiovascular autonomic neuropathy affects the vagal nerve first, resulting in parasympathetic dysfunction with elevated resting heart rate and impaired heart rate variability as the earliest manifestations. For more information, refer to **page 1405** of the *Continuum* article "Diabetic Neuropathies."

17 The preferred response is **D (80%).** The likelihood of developing treatment-induced neuropathy of diabetes is directly proportional to the magnitude and rate of hemoglobin A_{1c} change. A decrease in hemoglobin A_{1c} of greater than 4% over 3 months has an absolute risk of greater than 80%, reaching close to 100% if the decrease is 7% or higher. For more information, refer to **page 1414** of the *Continuum* article "Diabetic Neuropathies."

ARTICLE 6: INFECTIOUS NEUROPATHIES

18 The preferred response is **A (ocular involvement)**. A skin eruption on the tip or side of the nose in someone with herpes zoster is associated with an 80% likelihood of developing ocular involvement. For more information, refer to **pages 1420** to **1421** of the *Continuum* article "Infectious Neuropathies."

19 The preferred response is **C (cytomegalovirus)**. This patient's clinical presentation is typical of cauda equina syndrome, and the neutrophilic pleocytosis in the CSF indicates that it is inflammatory. Polyradiculitis is a characteristic manifestation of cytomegalovirus infection in patients with human immunodeficiency virus (HIV) infection. For more information, refer to **pages 1423** to **1424** of the *Continuum* article "Infectious Neuropathies."

20 The preferred response is **D (*Mycobacterium leprae*)**. Tender, beaded, thickened nerves are pathognomonic of neuropathy due to leprosy. For more information, refer to **pages 1431** to **1432** of the *Continuum* article "Infectious Neuropathies."

21 The preferred response is **C (distal symmetric polyneuropathy).** Distal symmetric predominantly sensory polyneuropathy is the most common type of peripheral nervous system disorder in patients with human immunodeficiency virus (HIV) infection. For more information, refer to **page 1424** of the *Continuum* article "Infectious Neuropathies."

ARTICLE 7: TOXIC NEUROPATHIES

22 The preferred response is **B (cisplatin).** This patient is presenting with "coasting," or worsening of the neuropathy, for months after the chemotherapy has been stopped. Coasting is characteristically seen with chemotherapy-induced peripheral neuropathy due to platins, including cisplatin, carboplatin, and oxaliplatin. For more information, refer to **page 1454** of the *Continuum* article "Toxic Neuropathies."

23 The preferred response is **B (duloxetine).** The American Society of Clinical Oncology recommends duloxetine as first-line therapy for neuropathic pain because it has the best evidence in patients with chemotherapy-induced peripheral neuropathy. For more information, refer to **pages 1456** to **1457** of the *Continuum* article "Toxic Neuropathies."

ARTICLE 8: NUTRITIONAL NEUROPATHIES

24 The preferred response is **D (B_6 [pyridoxine]).** Vitamin B_6 (pyridoxine) toxicity can cause a sensory neuronopathy. For more information, refer to **pages 1469** to **1470** of the *Continuum* article "Nutritional Neuropathies."

25 The preferred response is **E (B_{12} [cobalamin])**. Nitrous oxide inactivates cobalamin by oxidizing its cobalt core, so nitrous oxide toxicity causes the same symptoms and signs as vitamin B_{12} (cobalamin) deficiency. For more information, refer to **pages 1471** to **1472** of the *Continuum* article "Nutritional Neuropathies."

26 The preferred response is **A (anti-intrinsic factor antibodies).** Anti-intrinsic factor antibodies have high specificity but low sensitivity for pernicious anemia. Homocysteine levels can be elevated in deficiency of either vitamin B_{12} (cobalamin) or vitamin B_9 (folate). Antiparietal cell antibodies, mean corpuscular volume, and pepsinogen levels are nonspecific. For more information, refer to **pages 1473** to **1474** of the *Continuum* article "Nutritional Neuropathies."

27 The preferred response is **A (B_1 [thiamine]).** Thiamine deficiency can cause a rapidly progressive peripheral polyneuropathy that mimics Guillain-Barré syndrome. For more information, refer to **page 1477** of the *Continuum* article "Nutritional Neuropathies."

ARTICLE 9: PARAPROTEINEMIC NEUROPATHIES

28 The preferred response is **D (severely prolonged distal latencies).** This patient has clinical features and laboratory studies consistent with distal acquired demyelinating symmetric neuropathy (DADS) with monoclonal protein. The classic electrodiagnostic finding in patients with DADS with monoclonal protein, many of whom have IgM anti-myelin-associated glycoprotein (MAG) antibodies, is severely prolonged motor distal latencies. This characteristic finding is consistent with length-dependent demyelination. For more information, refer to **page 1497** of the *Continuum* article "Paraproteinemic Neuropathies."

29 The preferred response is **E (IgM).** Fifty percent to 75% of paraproteinemic neuropathies occur with the presence of an IgM subtype. For more information, refer to **page 1495** of the *Continuum* article "Paraproteinemic Neuropathies."

30 The preferred response is **E (rituximab).** This patient's clinical features are most consistent with a diagnosis of CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies). A 2020 multicenter trial demonstrated that IV immunoglobulin (IVIg) and rituximab-based regimens were the most effective therapies in patients with CANOMAD. Therefore, in this patient who had no response to an IVIg trial, rituximab would be the most appropriate treatment. For more information, refer to **page 1503** of the *Continuum* article "Paraproteinemic Neuropathies."

ARTICLE 10: HEREDITARY NEUROPATHIES

31 The preferred response is **E (hereditary neuropathy with liability to pressure palsies [HNPP])**. HNPP is associated with prolonged distal motor latencies and conduction block at compressible sites. For more information, refer to **pages 1516** to **1517** of the *Continuum* article "Hereditary Neuropathies."

32 The preferred response is **D (serine palmitoyltransferase)**. This patient has distal loss of pain sensation and autonomic symptoms typical of hereditary sensory and autonomic neuropathies, a group of hereditary neuropathies most often caused by variations in genes coding for subunits of serine palmitoyltransferase, which is involved in the synthesis of sphingolipids. For more information, refer to **page 1527** of the *Continuum* article "Hereditary Neuropathies."

ARTICLE 11: AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

33 The preferred response is **E (spastic dysarthria).** Patients with primary lateral sclerosis tend to have a more rapid progression and have involvement of upper limb and bulbar muscles compared with patients with hereditary spastic paraplegia. For more information, refer to **page 1543** of the *Continuum* article "Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases."

34 The preferred response is **B (*C9orf72*).** This patient has clinical features that suggest a diagnosis of amyotrophic lateral sclerosis with frontotemporal dementia. Patients who have a co-occurrence of these two disorders are more likely to have an underlying genetic variation; a *C9orf72* repeat expansion is the most common cause. For more information, refer to **page 1549** of the *Continuum* article "Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases."

35 The preferred response is **B (liver function).** Riluzole can cause elevated transaminases and can rarely cause acute liver failure. Therefore, patients who are started on riluzole should have regular monitoring of liver function tests (monthly for the first 3 months and then every 3 months thereafter). For more information, refer to **page 1551** of the *Continuum* article "Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases."

36 The preferred response is **B (mechanical insufflation-exsufflation)**. The patient's pulmonary function tests are significant for a decreased cough peak flow of 250 L/min. American Academy of Neurology guidelines recommend that mechanical insufflation-exsufflation be initiated when cough peak flow is less than 270 L/min. The patient does not meet the criteria to begin noninvasive ventilation. For more information, refer to **page 1553** of the *Continuum* article "Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases."

ARTICLE 12: SPINAL MUSCULAR ATROPHY

37 The preferred response is **B (nusinersen)**. Nusinersen and risdiplam modulate the splicing of the *SMN2* pre-mRNA, resulting in increased production of full-length SMN protein. Onasemnogene abeparvovec increases the production of full-length survival motor neuron (SMN) protein by introducing the *SMN1* gene copy. All three of these agents are approved by the US Food and Drug Administration (FDA) for the treatment of spinal muscular atrophy. Amifampridine blocks presynaptic potassium channels, prolonging the action potential. Salbutamol is a β_2-adrenoreceptor agonist that has also been proposed for the treatment of spinal muscular atrophy. Reldesemtiv slows the rate of calcium release from the troponin complex of fast skeletal muscle fibers. These three agents are not FDA approved for the treatment of spinal muscular atrophy. For more information, refer to **pages 1574** to **1579** of the *Continuum* article "Spinal Muscular Atrophy."

38 The preferred response is **C (onasemnogene abeparvovec)**. Onasemnogene abeparvovec increases the production of full-length survival motor neuron (SMN) protein by introducing the *SMN1* gene copy. Nusinersen and risdiplam modulate the splicing of the *SMN2* pre-RNA, resulting in increased production of full-length SMN protein. All three of these agents are approved by the US Food and Drug Administration (FDA) for the treatment of spinal muscular atrophy. Amifampridine blocks presynaptic potassium channels, prolonging the action potential. Reldesemtiv slows the rate of calcium release from the troponin complex of fast skeletal muscle fibers. These two agents are not FDA approved for the treatment of spinal muscular atrophy. For more information, refer to **pages 1574** to **1579** of the *Continuum* article "Spinal Muscular Atrophy."

39 The preferred response is **C (nusinersen)**. Nusinersen is administered intrathecally. Celecoxib and risdiplam are administered orally. For more information, refer to **pages 1574** to **1579** of the *Continuum* article "Spinal Muscular Atrophy."

40 The preferred response is **D (patellar)**. As spinal muscular atrophy progresses, the patellar reflexes are typically the first muscle stretch reflex to be lost. For more information, refer to **page 1568** of the *Continuum* article "Spinal Muscular Atrophy."

LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Peripheral Nerve and Motor Neuron Disorders issue, participants will be able to:

- **Initiate diagnostic evaluation in patients with suspected peripheral nerve disease by applying a framework for clinical diagnosis**
- **Discuss the clinical features, diagnostic criteria, differential diagnosis, pathogenesis, prognosis, and insights into the current and future diagnostic and therapeutic interventions of Guillain-Barré syndrome**
- **Identify the types of chronic demyelinating neuropathies and differentiate and treat immune-mediated demyelinating neuropathies**
- **Identify the common causes of autoimmune axonal neuropathy and develop appropriate clinical evaluation and management strategies based on subtype**
- **Diagnose and manage the spectrum of peripheral neuropathies associated with diabetes**
- **Discuss the infectious causes of peripheral neuropathies and the types of neuropathies associated with them**
- **Perform the clinical diagnosis, workup, and management of the most clinically relevant toxic neuropathies**
- **Discuss the clinical presentation, evaluation, and management of peripheral neuropathies caused by nutritional deficiencies**
- **Identify common clinical phenotypic, electrophysiologic, and hematologic features of each paraproteinemic neuropathy and tailor the appropriate diagnostic investigation and multidisciplinary treatment approach**
- **Guide the clinical evaluation of patients with suspected hereditary neuropathy and discuss the major clinical phenotypes and common genotypes of hereditary neuropathies**
- **Describe the clinical spectrum, diagnostic process, evolving genetic landscape, and approach to management for amyotrophic lateral sclerosis**
- **Discuss the diagnostic assessment of individuals with spinal muscular atrophy, available treatment options, and key outcome measures**
- **Identify the role of multidisciplinary care in the management of patients with neuromuscular disorders**

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Peripheral Nerve and Motor Neuron Disorders issue covers the following core competencies:

- **Patient Care and Procedural Skills**
- **Medical Knowledge**
- **Practice-Based Learning and Improvement**
- **Interpersonal and Communication Skills**
- **Professionalism**
- **Systems-Based Practice**

LIST OF ABBREVIATIONS

Peripheral Nerve and Motor Neuron Disorders

AAN	American Academy of Neurology
ACE2	Angiotensin-converting enzyme 2
ACTH	Adrenocorticotropic hormone
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
ALT	Alanine aminotransferase
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor-sensory axonal neuropathy
ANCA	Antineutrophil cytoplasmic autoantibody
ANNA-1	Antineuronal nuclear antibody type 1
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
CANDA	Chronic ataxic neuropathy with anti-disialosyl IgM antibodies
CANOMAD	Chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin IgM paraprotein, cold agglutinins, and disialosyl antibodies
CANVAS	Cerebellar ataxia with neuropathy and vestibular areflexia syndrome
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CIPN	Chemotherapy-induced peripheral neuropathy
CMAP	Compound muscle action potential CSF cerebrospinal fluid
CMT	Charcot-Marie-Tooth disease
CMV	Cytomegalovirus
COPM	Canadian Occupational Performance Measure
COVID-19	Coronavirus disease 2019
CRMP-5	Collapsin response mediator protein-5
CSF	Cerebrospinal fluid
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DNA	Deoxyribonucleic acid
DSPN	Distal symmetric polyneuropathy
EAN	European Academy of Neurology
EGRIS	Erasmus GBS Respiratory Insufficiency Score
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
EU	European Union
FDA	US Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
FTD	Frontotemporal dementia
FVC	Forced vital capacity
GAD65	Glutamic acid decarboxylase 65
GBS	Guillain-Barré syndrome
GPA	Granulomatosis with polyangiitis
HAART	Highly active antiretroviral therapy
HER-K	Human endogenous retrovirus-K
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Section 2
HIV	Human immunodeficiency virus
HNPP	Hereditary neuropathy with liability to pressure palsies
HSAN	Hereditary sensory and autonomic neuropathies
HSP	Hereditary spastic paraparesis
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
IgM	Immunoglobulin M
IM	Intramuscular
INCAT	Inflammatory Neuropathy Cause and Treatment
I-RODS	Inflammatory Rasch-built Overall Disability Scale
IV	Intravenous
IVIg	IVIg
LMN	Lower motor neuron
MAC	Membrane attack complex
MADSAM	Multifocal acquired demyelinating sensory and motor neuropathy
MAG	Myelin-associated glycoprotein
MFM	Motor Function Measurement
MGUS	Monoclonal gammopathy of undetermined significance
MMN	Multifocal motor neuropathy
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MRN	Magnetic resonance neurography
mRNA	Messenger ribonucleic acid
MuSK	Muscle-specific kinase
NCS	Nerve conduction studies
PAN	Polyarteritis nodosa
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein-1
PD-L1	Ligand of PD-1
PET	Positron emission tomography
PLEX	Plasma exchange
PLS	Primary lateral sclerosis
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skins changes
PRES	Posterior reversible encephalopathy
QSART	Quantitative sudomotor axon reflex testing
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SLE	Systemic lupus erythematosus
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SNAP	Sensory nerve action potential
SNRI	Serotonin norepinephrine reuptake inhibitor
SSA	Sjögren syndrome A
SSB	Sjögren syndrome B
STIR	Short tau inversion recovery
SWI	Susceptibility-weighted imaging
TSH	Thyroid-stimulating hormone
UMN	Upper motor neuron
VEGF	Vascular endothelial growth factor
VZV	Varicella-zoster virus
WHO	World Health Organization

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PERIPHERAL NERVE AND MOTOR NEURON DISORDERS

ARTICLE 1: LOCALIZATION AND DIAGNOSTIC EVALUATION OF PERIPHERAL NERVE DISORDERS

Peter H. Jin, MD. Continuum (Minneap Minn). October 2023;
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ABSTRACT

OBJECTIVE:

This article provides a framework for the initial evaluation of patients with suspected peripheral nerve disease. The key clinical elements of peripheral nerve diseases can help the practicing neurologist differentiate among peripheral neuropathies with similar presentations.

LATEST DEVELOPMENTS:

The wide range of peripheral nerve diseases with similar clinical presentations can pose a diagnostic challenge. The large array of available testing modalities (including imaging and electrodiagnostic, autonomic, laboratory, biopsy, and genetic testing) further complicates clinical decision making. Recent developments (eg, discovery of new autoantibodies, genetic variations, and histopathologic techniques) across the peripheral neuropathy spectrum have resulted in an increased need to evaluate patients logically and with a tailored diagnostic approach.

ESSENTIAL POINTS:

A careful approach that focuses on key clinical elements combined with an understanding of purposeful diagnostic testing can lead to a successful diagnosis of peripheral nerve diseases.

KEY POINTS

- The clinical approach to peripheral nerve disorders should focus on identifying specific clinical elements in the history and examination that include onset, pace of progression, modalities affected, anatomic distribution, and affected nerve fiber types.
- Diabetic sensory polyneuropathy is an acquired, chronic, slowly progressive, length-dependent, sensory-predominant, mixed large and small fiber, primarily axonal polyneuropathy. This is a pattern commonly seen in polyneuropathies caused by toxic and metabolic etiologies.

- Red flag findings for peripheral nerve disorders include acute to subacute onset with rapid progression, motor-predominant involvement, early involvement of proprioception (early sensory ataxia), bulbar involvement, and a multifocal or non–length-dependent distribution.
- Positive sensory symptoms often represent an acquired cause of sensory polyneuropathy, whereas the absence of positive sensory symptoms is commonly encountered in genetic neuropathies.
- Subtle findings of motor weakness in patients with chronic, sensory-predominant, axonal polyneuropathies may include mild toe flexor and toe extensor weakness.
- Prominent symptoms of chronic dysautonomia in a patient with an idiopathic neuropathy should prompt evaluation for amyloid neuropathy.
- Vibration sense testing with a quantitative tool such as a Rydel-Seiffer tuning fork allows for more objective measurements that can be tracked over time and correlate more directly to electrodiagnostic testing.
- Peripheral nerve disease is unlikely in older adult patients with isolated findings of absent ankle reflexes and mild decreased vibration sense in the feet without other associated historical or examination elements.
- Skin and joint examination can reveal key diagnostic elements in diseases of peripheral nerves. Ideally, patients should change into a gown to allow for inspection of the proximal extremeties and trunk.
- Patients with potential peripheral nerve disorders may have multiple diagnoses that overlap. Although this overlap is most common with other peripheral nerve disorders, disorders of the central nervous system can also manifest with symptoms and signs traditionally associated with the peripheral nervous system.
- Non-neurologic disorders can mimic peripheral nerve disease and should be considered in the presence of inconsistent neurologic examination findings and electrodiagnostic testing.
- Except in clinically definitive cases, electrodiagnostic testing should be considered for most patients with peripheral nerve disease because there are many mimics with similar clinical presentations. Electrodiagnostic testing often identifies the presence of multiple concomitant diseases.
- All patients with sensory peripheral neuropathy should be tested for fasting blood glucose, vitamin B_{12} levels, and serum electrophoresis with immunofixation.
- Patients with idiopathic sensorimotor polyneuropathy, bilateral carpal tunnel syndrome, lumbar stenosis, and dysautonomia should be considered for amyloid testing including genetic testing for hereditary transthyretin amyloidosis.
- Imaging studies are most helpful when clinical suspicion for a specific diagnosis is high but electrodiagnostic testing results are ambiguous or inconclusive.
- Although neuromuscular ultrasound provides greater resolution of peripheral nerve anatomy, it is currently limited to the study of superficial nerves. The study of deeper (generally more proximal) peripheral nerves can be accomplished via MRI neurography.
- Nerve biopsy is most useful in cases of suspected vasculitic neuropathy and neurolymphomatosis. It can also be useful for the diagnosis of nerve sheath tumors, amyloidosis, sarcoidosis, and leprosy.

ARTICLE 2: GUILLAIN-BARRÉ SYNDROME

Ali A. Habib, MD; Waqar Waheed, MD. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1327–1356.

ABSTRACT

OBJECTIVE:

This article summarizes the clinical features, diagnostic criteria, differential diagnosis, pathogenesis, and prognosis of Guillain-Barré syndrome (GBS), with insights into the current and future diagnostic and therapeutic interventions for this neuromuscular syndrome.

LATEST DEVELOPMENTS:

GBS is an acute, inflammatory, immune-mediated polyradiculoneuropathy that encompasses many clinical variants and divergent pathogenic mechanisms that lead to axonal, demyelinating, or mixed findings on electrodiagnostic studies. The type of antecedent infection, the development of pathogenic cross-reactive antibodies via molecular mimicry, and the location of the target gangliosides affect the subtype and severity of the illness. The data from the International GBS Outcome Study have highlighted regional variances, provided new and internationally validated prognosis tools that are beneficial for counseling, and introduced a platform for discussion of GBS-related open questions. New research has been undertaken, including research on novel diagnostic and therapeutic biomarkers, which may lead to new therapies.

ESSENTIAL POINTS:

GBS is among the most frequent life-threatening neuromuscular emergencies in the world. At least 20% of patients with GBS have a poor prognosis and significant residual deficits despite receiving available treatments. Research is ongoing to further understand the pathogenesis of the disorder, find new biomarkers, and develop more effective and specific treatments.

KEY POINTS

- Demyelinating forms of Guillain-Barré syndrome (GBS) with a respiratory prodrome dominate in Europe and North America whereas axonal subtypes following a diarrheal illness are more common in Asia, particularly in Bangladesh and northern China.
- A small increased risk of GBS occurs after the Ad.26.COV2.S COVID-19 vaccine but not the mRNA vaccines.
- The GBS prodrome is followed by a progressive phase with the development of neuropathy symptoms, which by definition should not progress beyond 4 weeks.
- Treatment-related fluctuations can occur in up to 10% of patients with GBS and often respond to retreatment with the previously administered immunomodulatory therapy.
- If a patient with an acute neuropathy has three or more relapses or progression beyond 8 weeks, then the diagnosis of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy should be considered.
- Sensory symptoms help exclude pure motor disorders such as motor neuron disease, myopathy, or myasthenia gravis in patients with possible GBS; however, objective sensory loss is mild and delayed.
- Weakness is accompanied by hyporeflexia or areflexia in approximately 90% of patients with GBS; however, this finding may be delayed by up to a week, and some patients with acute motor axonal neuropathy might have normal or even exaggerated reflexes.
- Severe weakness of respiratory muscles, particularly the diaphragm, necessitates ventilatory support in 10% to 30% of patients with GBS.
- Acute motor-sensory axonal neuropathy is often clinically more severe than other variants of GBS, with frequent autonomic and cranial nerve dysfunction.
- Acute motor axonal neuropathy has two patterns of recovery: quick recovery within days because of the resolution of conduction block, or slow and poor recovery because of extensive axonal degeneration.
- Miller Fisher syndrome includes a spectrum of disorders with reactivity against specific antiganglioside GQ1b antibodies in approximately 85% to 90% of patients.
- The complete form of Miller Fisher syndrome, characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia, is more common in East Asia, particularly in Japan.
- Bickerstaff brainstem encephalitis is a Miller Fisher syndrome–related disorder, where, in addition to ataxia and ophthalmoparesis, patients develop impaired consciousness and paradoxical hyperreflexia because of involvement of reticular formation and pyramidal tracts.
- The localization of the target ganglioside antigens, as well as the binding specificity of the antiglycolipid antibodies, are associated with distinctive clinical subtypes of GBS.

- In acute inflammatory demyelinating polyradiculoneuropathy, demyelination and multifocal perivascular and endoneurial T-cell infiltration ensue along the length of the nerve, particularly early in the proximal nerve roots and distal nerve segments where the blood-nerve barrier is weak.
- Acute motor axonal neuropathy is characterized by the presence of IgG anti-GM1 or anti-GD1a autoantibodies, which bind to the nodal axolemma, leading to complement activation and membrane attack complex formation.
- Mild CSF pleocytosis of 10 to 20 cells/mm^3 is seen in up to 5% of patients with GBS. The presence of marked pleocytosis of more than 50 cells/mm^3 should prompt the evaluation for alternative causes.
- Given that intravenous immunoglobulin (IVIg) therapy can raise CSF protein and white blood cell counts, CSF analysis following the start of IVIg therapy can be difficult to interpret.
- Electrodiagnostic studies performed early in the course of GBS may be normal or show subtle or nonspecific abnormalities. Often, a repeat study performed several weeks later is required for definitive characterization of the disease subtype.
- Spinal MRI can demonstrate thickening and enhancement of intrathecal spinal nerve roots, supporting a diagnosis of GBS with a sensitivity of 83%, especially in young children in whom clinical and electrophysiologic examinations can be difficult.
- The following factors may prompt admission of patients with GBS to the intensive care unit: dysautonomia, bulbar dysfunction, severe or rapidly worsening weakness, and evolving respiratory distress.
- A score of more than 4 on the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score suggests a high (≥65%) risk of respiratory failure, which warrants monitoring in an intensive care setting.
- Patients with GBS who have reached a clinical nadir or have experienced a modest decline over days with continued ability to ambulate may be treated in the general ward with continuous monitoring.
- Intubation of patients with GBS and respiratory decline should be performed electively when possible, as emergency intubation can provoke dramatic blood pressure shifts and profound bradycardia by the introduction of an endotracheal tube in patients with dysautonomia.
- Noninvasive ventilation is usually insufficient for patients with GBS and respiratory decline and raises the risk of emergency intubation and aggravation of dysautonomia.
- Clinical trials have shown that IVIg and plasma exchange are effective in reducing the time to recovery in patients with GBS who are unable to walk a distance of 10 meters independently.
- Repeating IVIg or plasma exchange for absence of clinical response after initial treatment for GBS provides no additional benefit.
- While the electrophysiologic findings are similar between acute inflammatory demyelinating polyradiculoneuropathy and acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), patients with acute-onset CIDP are more likely to have sensory deficits or ataxia and less likely to have had a preceding infectious illness, autonomic nervous system involvement, facial weakness, or need for mechanical ventilation.
- Two validated prognostic models, the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score and modified Erasmus GBS Outcome Score, are available in a user-friendly online version to guide the need for mechanical ventilation within a week of admission and the functional outcome of patients with GBS at 6 months, respectively.
- The overall mortality rate of patients with GBS varies from 3% to 7% overall and is around 20% in patients who become ventilator dependent.

ARTICLE 3: CHRONIC IMMUNE-MEDIATED DEMYELINATING NEUROPATHIES

Karissa Gable, MD. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1357-1377.

ABSTRACT

OBJECTIVE:

This article is an overview of chronic demyelinating neuropathies and highlights the phenotypic categorization, diagnosis, and treatment of chronic immune-mediated neuropathies. The clinical and diagnostic characteristics of other chronic demyelinating neuropathies that are common mimics of immune-mediated neuropathies are also discussed.

LATEST DEVELOPMENTS:

The underlying pathophysiology of chronic demyelinating neuropathies is heterogeneous, and components of both humoral and cellular immune responses are thought to play a role in the immune-mediated types of chronic demyelinating neuropathy. The role of the humoral response is highlighted with a specific focus on the relatively recent discovery of antibody-mediated antinodal and paranodal demyelinating neuropathies. Additionally, new diagnostic criteria for some of the chronic demyelinating neuropathies, as well as ways to differentiate chronic inflammatory demyelinating polyradiculoneuropathy from other chronic demyelinating polyneuropathies, are discussed.

ESSENTIAL POINTS:

Chronic demyelinating neuropathies can present with overlapping clinical characteristics with seemingly subtle variations. It is clinically important to differentiate these types of neuropathies because the treatment and management can vary and affect prognosis.

KEY POINTS

- Accurate diagnosis of chronic demyelinating neuropathies is important because some types, particularly chronic inflammatory neuropathies, can be functionally debilitating if not diagnosed and treated properly.
- Typical chronic inflammatory demyelinating polyneuropathy (CIDP) accounts for approximately 50% to 60% of all cases and presents with symmetric proximal and distal upper and lower extremity weakness and sensory loss affecting at least two limbs with areflexia that is progressive over a time period greater than 2 months.
- Up to 16% of patients with CIDP can present with acute or subacute CIDP, and clinical monitoring is required to tell if the diagnosis is in fact CIDP.
- CIDP variants can have a combination of motor and sensory findings that are asymmetric, purely motor, purely sensory, focal, or distally patterned.
- Multifocal CIDP is a variant of CIDP that can present clinically with asymmetric weakness and sensory loss affecting the upper or lower extremities.
- The underlying pathophysiology of CIDP, both typical CIDP and the CIDP variants, involves the humoral and cellular immune-mediated systems.
- Response to treatment, spinal fluid testing, antibody testing, imaging with MRI or ultrasonography, and rarely nerve biopsy are supportive investigations that can be performed to confirm the diagnosis of CIDP.

- It is recommended that improvements be noted objectively on at least one measure of disability and on one impairment scale following treatment to demonstrate adequate support of the diagnosis of CIDP, particularly in cases of possible CIDP.
- Both MRI and ultrasonography can be used as imaging modalities to support the diagnosis of CIDP.
- MRI evidence of focal nerve enlargement, hyperintensity, or enhancement are not specific to CIDP and can also be seen in hereditary neuropathy and malignancy.
- CIDP is characterized by albuminocytologic dissociation or a normal CSF nucleated cell count and elevated protein levels.
- Up to one-half of patients initially diagnosed with CIDP may be ultimately found to have an alternative diagnosis.
- Greater than 50% of patients who present with a distal demyelinating neuropathy associated with IgM monoclonal gammopathy develop antibodies against myelin-associated glycoprotein.
- Approximately 10% of patients meeting the electrodiagnostic criteria for CIDP have antibodies against node of Ranvier nodal and paranodal proteins.
- Anti-GM1 antibodies are seen in some but not all patients with multifocal motor neuropathy, and the absence of GM1 antibodies does not exclude the diagnosis.
- Pain is often a more prominent feature of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome–related neuropathy compared with CIDP.
- Treatment of typical CIDP and its variants is similar and includes IVIg, steroids, or plasma exchange as first-line induction and maintenance therapies.
- Transition from IVIg to subcutaneous immunoglobulin in the treatment of immune-mediated neuropathies can occur in a 1:1 dosing transition.
- Rituximab treatment appears to be the most effective treatment for patients with antiparanodal and antinodal antibody immune-mediated neuropathies.
- Several randomized controlled trials support the use of IVIg as a first-line treatment for multifocal motor neuropathy.

ARTICLE 4: AUTOIMMUNE AXONAL NEUROPATHIES

Jennifer A. Tracy, MD. Continuum (Minneap Minn). October 2023;
29 (5 Sleep Neurology):1378–1400.

ABSTRACT

OBJECTIVE:

This article reviews autoimmune axonal neuropathies, their characteristic clinical features, disease and antibody associations, appropriate ancillary testing, treatment, and prognosis.

LATEST DEVELOPMENTS:

In 2021, the American College of Rheumatology and the Vasculitis Foundation released new summary guidelines for the treatment of antineutrophil cytoplasmic autoantibody–associated vasculitides. In addition, novel autoantibodies have been recently identified; they are often paraneoplastic and associated with axonal neuropathies.

ESSENTIAL POINTS:

Recognition of autoimmune axonal neuropathies is important because of the potential for effective treatment to either reverse deficits or slow the progression of disease. It is necessary to properly assess for associations with other systemic disorders (eg, systemic vasculitis,

connective tissue disease, neoplasm) so that adequate treatment for both neurologic and non-neurologic aspects of the disease can be initiated.

KEY POINTS

- Vasculitis can be systemic or limited and can exclusively involve the peripheral nerves. Peripheral neuropathy can also be the presenting sign of primary systemic vasculitis.
- Clues for vasculitic neuropathy include subacute onset, mixed sensorimotor features, profound sensory loss, and multifocality.
- Later in the disease course, the diagnosis of vasculitic neuropathy may be clouded by multiple overlapping mononeuropathies leading to a more symmetric length-dependent clinical examination.
- Myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody is commonly associated with microscopic polyangiitis.
- Proteinase 3 antineutrophil cytoplasmic autoantibody is commonly associated with granulomatosis with polyangiitis.
- For patients presenting with long-standing severe neuropathy, a history of step-wise progression should be queried because neurophysiology may only disclose nonspecific length-dependent findings.
- Nerve biopsy can be diagnostic in patients with suspected vasculitic neuropathy, but a clinically affected nerve must be selected for biopsy.
- Myeloperoxidase–perinuclear antineutrophil cytoplasmic autoantibody, asthma, and eosinophilia are commonly associated with eosinophilic granulomatosis with polyangiitis.
- Polyarteritis nodosa and associated neuropathy can develop in the context of hepatitis B infection.
- Although radiculoplexus neuropathies are more commonly present in patients with mild diabetes, a nondiabetic form also exists. Nondiabetic lumbosacral radiculoplexus neuropathy is usually monophasic with gradual, sometimes incomplete recovery.
- Although postsurgical neuropathies are often related to stretch or direct trauma, they are sometimes inflammatory.
- Neuralgic amyotrophy is usually monophasic; when repeated events occur, suspicion should be raised for hereditary brachial plexus neuropathy.
- Between 5% and 20% percent of patients with Sjögren syndrome have some type of peripheral nervous system complication.
- Sjögren syndrome is associated with a wide array of neuropathic complications, most characteristically a sensory neuronopathy. Treatment responsiveness of Sjögren neuropathy is variable, and results of treatment are poor in cases of sensory neuronopathy.
- Rheumatoid arthritis is associated with many types of structural nerve damage (eg, from cervical spine disease or carpal tunnel syndrome) in addition to inflammatory mechanisms.
- Tumor necrosis factor α inhibitor therapy for rheumatoid arthritis may trigger the development of neuropathy.
- Systemic lupus erythematosus may be associated with an axonal, asymmetric, or symmetric sensory or sensorimotor polyneuropathy. Many patients with systemic lupus erythematosus and polyneuropathy may have alternative causes for their polyneuropathy.
- Paraneoplastic neuropathies usually present acutely to subacutely and are often asymmetric. Antineuronal nuclear antibody type 1 (ANNA-1; anti-Hu), collapsin response mediator protein-5 (CRMP-5; also known as *anti-CV2*), and amphiphysin antibodies are among the most common paraneoplastic autoantibodies associated with neuropathy.

ARTICLE 5: DIABETIC NEUROPATHIES

Melissa A. Elafros, MD, PhD; Brian C. Callaghan, MD, MS, FAAN. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1401–1417.

ABSTRACT

OBJECTIVE:

This article provides an up-to-date review of the diagnosis and management of the most common neuropathies that occur in patients with diabetes.

LATEST DEVELOPMENTS:

The prevalence of diabetes continues to grow worldwide and, as a result, the burden of diabetic neuropathies is also increasing. Most diabetic neuropathies are caused by hyperglycemic effects on small and large fiber nerves, and glycemic control in individuals with type 1 diabetes reduces neuropathy prevalence. However, among people with type 2 diabetes, additional factors, particularly metabolic syndrome components, play a role and should be addressed. Although length-dependent distal symmetric polyneuropathy is the most common form of neuropathy, autonomic syndromes, particularly cardiovascular autonomic neuropathy, are associated with increased mortality, whereas lumbosacral radiculoplexus neuropathy and treatment-induced neuropathy cause substantial morbidity. Recent evidence-based guidelines have updated the recommended treatment options to manage pain associated with distal symmetric polyneuropathy of diabetes.

ESSENTIAL POINTS:

Identifying and appropriately diagnosing the neuropathies of diabetes is key to preventing progression. Until better disease-modifying therapies are identified, management remains focused on diabetes and metabolic risk factor control and pain management.

KEY POINTS

- The prevalence of diabetic neuropathies will continue to grow as the burden of diabetes increases worldwide and, until disease-modifying treatments are identified, management is reliant on addressing factors that increase the risk of neuropathy and neuropathy-related complications.
- Neuropathy in diabetes can present with length-dependent, autonomic, focal, or generalized signs and symptoms.
- Distal symmetric polyneuropathy is the most common neuropathy in diabetes and presents with length-dependent numbness, tingling, and pain. Neurologic examination should include assessment of both large and small fiber function as small fiber nerves are often affected first in distal symmetric polyneuropathy.
- Any form of chronically elevated blood glucose has been associated with the development of distal symmetric polyneuropathy, including prediabetes.
- Screening for comorbid medical conditions among people with neuropathy is essential. In addition to diabetes duration and severity, metabolic syndrome components, in particular central obesity, are also associated with an increased risk of distal symmetric polyneuropathy among people with type 2 diabetes.
- Electrodiagnostic testing is generally not recommended to confirm clinically diagnosed diabetic distal symmetric polyneuropathy unless the patient has features that are atypical, such as rapid onset, non–length-dependent symptoms, asymmetry, or motor-predominant symptoms.

- **Although glycemic control alone prevents the development of distal symmetric polyneuropathy among people with type 1 diabetes, it is insufficient in isolation among people with type 2 diabetes. Therefore, multiple interventions targeting metabolic syndrome components are necessary. Exercise has been associated with improvement in patient-reported symptoms.**
- **Distal symmetric polyneuropathy management is focused on risk factor reduction and pain management. The American Academy of Neurology guidelines recommend four classes of medications for neuropathic pain management.**
- **Opioids are not recommended for the treatment of painful diabetic distal symmetric polyneuropathy because limited data support their long-term effectiveness and the emerging downsides include death, overdose, abuse, and addiction.**
- **Setting reasonable expectations and performing regular assessment of a patient's pain level are essential to titrating medications for neuropathic pain control.**
- **Screening for cardiovascular autonomic neuropathy in patients with diabetes is critical since those with cardiovascular autonomic neuropathy are more than two times more likely to die than those without cardiovascular autonomic neuropathy.**
- **Symptoms of cardiovascular autonomic neuropathy often present late in the disorder with dizziness, orthostatic hypotension, and syncope.**
- **Risk factors for developing cardiovascular autonomic neuropathy include prolonged hyperglycemia but also include traditional cardiovascular risk factors such as age, hypertension, dyslipidemia, and central obesity.**
- **Patients with a history of microvascular complications of diabetes, such as distal symmetric polyneuropathy, should be screened for signs and symptoms of cardiovascular autonomic neuropathy. The Ewing battery can often be completed in the office with an ECG and blood pressure cuff.**
- **Among people with type 2 diabetes, targeting traditional cardiovascular risk factors as well as hyperglycemia is essential to reduce the incidence of cardiovascular autonomic neuropathy.**
- **Symptomatic management of cardiovascular autonomic neuropathy, particularly among patients with orthostatic hypotension, is critical. A multifaceted approach that includes stopping offending medications, increasing fluid and salt intake, and behavioral modifications is most effective.**
- **Patients with lumbosacral radiculoplexus neuropathy endorse sudden-onset pain in the hip or thigh followed by focal lower limb weakness that worsens over time. Symptoms slowly improve but can take up to 2 years to plateau, and few patients report returning to their prior neurologic baseline.**
- **Nerve conduction studies in a patient with diabetic lumbosacral radiculoplexus neuropathy will show low-amplitude compound muscle action potentials and sensory nerve action potentials as well as fibrillation potentials in muscles in a patchy pattern that does not localize to one nerve or nerve root. Findings will be asymmetric between lower limbs.**
- **There are currently no effective disease-modifying treatments for diabetic lumbosacral radiculoplexus neuropathy, and management is focused on pain management and adaptive devices to improve quality of life.**
- **Treatment-induced neuropathy of diabetes should be considered in an individual with diabetes who presents with acute or subacute pain in the setting of a rapid improvement in glycemic control. Symptoms are best localized to the small fiber nerves and present with burning, shocklike pain, allodynia, and hyperalgesia.**
- **Patients with treatment-induced neuropathy of diabetes should undergo screening for other microvascular complications as they often experience progression of retinopathy and nephropathy that needs to be appropriately monitored.**
- **Management of treatment-induced neuropathy of diabetes should focus on preventing neuropathy progression by stabilizing labile glycemic control, managing symptoms via neuropathic pain management, and preventing recurrence. Patients should be counseled that symptoms may improve but may not completely resolve.**
- **Prevention of treatment-induced neuropathy of diabetes by educating primary care providers and endocrinologists is essential to avoid fast drops in hemoglobin A_{1C} as this is a highly morbid neuropathy. Among patients with existing treatment-induced neuropathy, coordination with the patient's primary care provider or endocrinologist is essential to prevent neuropathy progression.**

ARTICLE 6: INFECTIOUS NEUROPATHIES

Aimee K. Boegle, MD, PhD; Pushpa Narayanaswami, MD, FAAN. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1418–1443.

ABSTRACT

OBJECTIVE:

This article discusses the clinical manifestations and management of infectious peripheral neuropathies.

LATEST DEVELOPMENTS:

Several infectious etiologies of peripheral neuropathy are well-recognized and their treatments are firmly established. The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with several central and peripheral nervous system manifestations, including peripheral neuropathies. Additionally, some COVID-19 vaccines have been associated with Guillain-Barré syndrome. These disorders are an active area of surveillance and research. Recent evidence-based guidelines have provided updated recommendations for the diagnosis and treatment of Lyme disease.

ESSENTIAL POINTS:

Infectious agents of many types (primarily bacteria and viruses) can affect the peripheral nerves, resulting in various clinical syndromes such as mononeuropathy or mononeuropathy multiplex, distal symmetric polyneuropathy, radiculopathy, inflammatory demyelinating polyradiculoneuropathy, and motor neuronopathy. Knowledge of these infections and the spectrum of peripheral nervous system disorders associated with them is essential because many have curative treatments. Furthermore, understanding the neuropathic presentations of these disorders may assist in diagnosing the underlying infection.

KEY POINTS

- Following acute infection, herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus remain dormant in sensory ganglia, with risk of future viral reactivation.
- Risk factors for the reactivation of the varicella-zoster virus and the development of zoster include age (>60 years), underlying human immunodeficiency virus (HIV) infection or malignancy, treatment with immunosuppressants, and organ transplantation.
- Postherpetic neuralgia is the most common complication of herpes zoster. Risk factors include older age, the intensity of pain at onset, the severity of the rash, involvement of the ophthalmic division of the trigeminal nerve, diabetes, and immunosuppression.
- Herpes zoster ophthalmicus is an ophthalmic emergency and can cause permanent visual loss. Urgent ophthalmologic evaluation is recommended.
- Herpes simplex virus type 2 can cause lumbosacral polyradiculitis with or without myelitis. Symptoms include radicular and perineal pain or paresthesia. Severe cases present with motor weakness and sphincter disturbances. Vesicular skin lesions can help determine the diagnosis.
- Cytomegalovirus (CMV) is the second most common infectious antecedent for Guillain-Barré syndrome (GBS) syndrome after *Campylobacter jejuni*. The presence of anti-GM2 antibodies is highly specific for post-CMV GBS.
- CMV infection in immunocompromised individuals can lead to several peripheral nerve syndromes including myelitis, radiculitis, brachial plexopathies, and mononeuritis multiplex.
- CMV polymerase chain reaction testing confirms the diagnosis of CMV-related disease and is useful in monitoring response to treatment.

- HIV is commonly associated with peripheral nerve disorders caused by the direct effect of the virus, other opportunistic diseases, or side effects from antiretroviral medications.
- The most common peripheral nerve disorder in HIV is painful, distal symmetric polyneuropathy.
- Nucleoside reverse transcriptase inhibitors (didanosine, stavudine, and zalcitabine), can cause antiretroviral toxic neuropathy. When possible, affected patients should attempt to transition to alternative antiretroviral therapies.
- In HIV-positive patients with painful sensory polyneuropathy, it is important to exclude alternative or additional etiologies such as diabetes mellitus, vitamin B_{12} and other nutritional deficiencies, concomitant drugs such as isoniazid, and alcohol-related polyneuropathy.
- HIV seroconversion can be associated with cranial neuropathies (especially affecting the facial nerve) and GBS. Mild lymphocytic pleocytosis differentiates this syndrome from typical GBS.
- Immune status in HIV correlates with the type of peripheral nerve disorder. For patients with HIV, inflammatory neuropathies occur at higher CD4 counts and opportunistic infections at lower CD4 counts.
- Diffuse infiltrative lymphocytosis syndrome is a hyperimmune response to HIV infection characterized by the expansion of $CD8^+$ lymphocytes. Patients present with multisystemic lymphocytic infiltration, which can involve peripheral nerves.
- A motor neuron syndrome resembling amyotrophic lateral sclerosis can occur rarely in HIV-infected patients. This syndrome presents subacutely and progresses more rapidly than amyotrophic lateral sclerosis.
- Mixed cryoglobulinemia is present in up to 50% of patients with hepatitis C and increases the risk of peripheral neuropathy.
- Vasculitis appears to be the underlying pathology in both cryoglobulin-positive and cryoglobulin-negative hepatitis C patients with peripheral neuropathy.
- Olfactory dysfunction in severe acute respiratory syndrome coronavirus 2 infection may occur in otherwise asymptomatic patients and may be the presenting symptom of COVID-19.
- A higher risk of GBS has been reported with the Ad26.COV2.S vaccine but not other COVID-19 vaccines.
- Leprosy remains a common cause of infectious neuropathy in the tropics and subtropics, with the highest incidence occurring in India, Brazil, and Indonesia.
- The host immune response determines the clinical presentation of leprosy. A robust cell-mediated response results in paucibacillary tuberculoid leprosy, whereas an ineffective humoral response results in multibacillary lepromatous leprosy.
- Classic symptoms of leprous neuropathy include anesthesia, inability to sweat, and patchy motor weakness. Painless skin ulcers may be present. Intraneural inflammation causes nerve thickening.
- Early diagnosis and treatment are essential to prevent leprosy-related deformities and disability. Clinicians in nonendemic areas should consider leprosy in the differential diagnosis of cryptogenic neuropathies, especially in patients from endemic areas.
- Lyme disease is the most common vector-borne illness in the United States and Europe, where ticks and spirochetes are endemic. Climate change is leading to a more widespread geographic dispersion of Lyme disease.
- Although facial neuropathy is the most frequent cranial neuropathy in early disseminated Lyme disease, patients can present with multiple cranial neuropathies.
- Early serologic testing for Lyme disease may return a false-negative result. When early testing is negative and clinical symptoms are suggestive, the clinical recommendation is to retest in 1 month from the start of symptoms.

ARTICLE 7: TOXIC NEUROPATHIES

Brendan L. McNeish, MD; Noah Kolb, MD. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1444–1468.

ABSTRACT

OBJECTIVE:

The purpose of this article is to provide an overview and update on the most clinically relevant toxic neuropathies.

LATEST DEVELOPMENTS:

Broadly, toxic neuropathies were previously quite rare with the notable exception of neuropathy from alcohol or older chemotherapeutics. The development of newer therapies, particularly immunotherapy to treat malignancy, has resulted in a substantial increase in the occurrence of toxic neuropathies that require timely recognition and treatment. The understanding of other toxic neuropathies continues to evolve, such as statin-induced neuropathy, which new evidence suggests is much less common than previously suspected.

ESSENTIAL POINTS:

Toxic neuropathies can be caused by medications, supplements, and recreational substances that injure peripheral nerves. Medications have evolved in the past 2 decades, as have the types of neuropathies that can be seen as related toxicities. In some areas of medicine, new classes and generations of drugs are associated with a lower incidence of toxic neuropathy.

KEY POINTS

- Immune checkpoint inhibitor-related neuropathy is projected to become more prevalent because more cancers are becoming eligible for immune checkpoint inhibitor therapy.
- Immune checkpoint inhibitor-related neuropathy can present with a broad spectrum of phenotypes determined by the components of the peripheral nervous system targeted by the immune system.
- Immune checkpoint inhibitor-related neuropathy incidence increases when ligand of programmed cell death protein-1 and cytotoxic T-lymphocyte-associated antigen 4 therapies are combined.
- In cases of severe sensory neuropathy or neuronopathy in patients on immune checkpoint inhibitors, it is important to screen for paraneoplastic syndromes.
- Because of phenotypic heterogeneity, recognizing the acute onset of neurologic deficits and temporal relationship to immune checkpoint therapy are critical for the diagnosis of an immune checkpoint inhibitor-related neuropathy.
- Because of the diversity of neurologic involvement, a standardized diagnostic and treatment algorithm is recommended in evaluating patients with suspected immune checkpoint inhibitor-related neuropathies.
- Selecting the correct treatment for immune checkpoint inhibitor-related neuropathy relies on accurately grading the severity of the presentation.
- Unlike other forms of Guillain-Barré syndrome, patients with immune checkpoint inhibitor-related acute inflammatory demyelinating polyradiculoneuropathy respond to treatment with corticosteroids and are more likely to have CSF pleocytosis.
- It is unclear whether immunosuppression for immune checkpoint inhibitor-related neuropathy changes cancer prognosis and whether rechallenge of immune checkpoint inhibitor therapy should be considered in these patients.
- Chemotherapy-induced peripheral neuropathy is the most common dose-limiting side effect of neurotoxic chemotherapy.

- The phenotype of chemotherapy-induced peripheral neuropathy varies widely depending on the causative agent.
- In patients suspected to have chemotherapy-induced peripheral neuropathy by history and examination, the laboratory evaluation for other causes can be simplified to include hemoglobin A_{1c}, vitamin B_{12}, and serum protein electrophoresis with immunofixation. Electrodiagnostic testing is generally not required in these patients.
- The most common neurotoxic chemotherapeutic medications that cause chemotherapy-induced peripheral neuropathy are taxanes, platins, vinca alkaloids, and bortezomib.
- Taxanes typically cause a sensory-predominant neuropathy that affects both the hands and feet.
- Duloxetine has the most supporting evidence for the treatment of neuropathic pain in chemotherapy-induced peripheral neuropathy.
- Chemotherapy-induced peripheral neuropathy management should be multidisciplinary, focusing on pain management, rehabilitation, and quality of life because there are no current disease-modifying therapies, and many cancer survivors will have a normal lifespan.
- Chloroquine can cause a vacuolar myopathy and sensorimotor polyneuropathy with some demyelinating features.
- A study published in 2022 suggests that statin-induced neuropathy is much less common than previously thought.
- Diabetes or prediabetes, vitamin deficiency, and alcohol misuse remain the most common identifiable causes of neuropathy in the United States.
- The primary mechanism of neuropathy associated with long-term use of high doses of isoniazid is related to vitamin B_6 deficiency.
- It can be challenging to differentiate human immunodeficiency virus (HIV) neuropathy from neuropathy caused by antiretroviral drugs, and the diagnosis can be aided by looking for other signs of toxicity.
- A comprehensive social and occupational history is important when heavy metal neuropathy is suspected.

ARTICLE 8: NUTRITIONAL NEUROPATHIES

Neeraj Kumar, MD. Continuum (Minneap Minn). October 2023;
29 (5 Sleep Neurology):1469–1491.

ABSTRACT

OBJECTIVE:

This article reviews the etiologies, presentations, and management of neuropathies related to nutritional deficiencies.

LATEST DEVELOPMENTS:

Peripheral neuropathy can be the predominant or only manifestation of certain nutrient deficiencies. Cognitive difficulties or involvement of other parts of the central nervous system, such as the optic nerve and spinal cord, may accompany nutritional peripheral neuropathies. In most patients, the nutritional deficiency may have a single predominant cause, but in some cases, multiple causes may coexist. Obesity, for unclear reasons, can be associated with nutrient deficiencies. The rising rates of bariatric surgery and the incidence of nutrient deficiencies following bariatric surgery make this a particularly relevant topic for neurologists.

ESSENTIAL POINTS:

Neuropathies caused by nutrient deficiencies are preventable with appropriate supplementation in high-risk situations. Early recognition and prompt treatment are essential to ensure an optimal outcome and minimize neurologic morbidity.

KEY POINTS

- The B-group vitamins whose deficiency is associated with neurologic disease include vitamin B_1 (thiamine), vitamin B_3 (niacin), vitamin B_6 (pyridoxine), vitamin B_9 (folic acid), and vitamin B_{12} (cobalamin).
- When multiple nutrient deficiencies coexist, both the central and peripheral nervous systems can be involved, and multiple causes of these deficiencies can be present.
- Vitamin B_{12}, folate, vitamin E, and copper deficiencies often have associated spinal cord involvement along with peripheral neuropathy.
- Except for manifestations caused by thiamine and folate deficiency, neurologic manifestations are generally seen in the late stages of malnutrition.
- Pernicious anemia may be accompanied by iron deficiency, increased risk of gastric cancer or carcinoid, and other autoimmune diseases such as autoimmune thyroiditis, Addison disease, vitiligo, and type 1 diabetes.
- Food-bound vitamin B_{12} malabsorption is particularly common in older adults because of the high incidence of atrophic gastritis; however, this is often unaccompanied by clinical manifestations, and the precise significance of subclinical vitamin B_{12} deficiency and its management is poorly understood.
- Typically, it takes 4 to 5 years of malabsorption to develop clinically apparent vitamin B_{12} deficiency because of large hepatic stores and minute daily losses.
- Nitrous oxide oxidizes the cobalt core of cobalamin and renders cobalamin inactive. In this setting, although low or low-normal vitamin B_{12} levels may be present, the pathophysiologic hallmark is a functionally inactive vitamin B_{12}, leading to a syndrome typical of vitamin B_{12} deficiency.
- The classic neurologic manifestation of vitamin B_{12} deficiency is a subacute combined degeneration of the spinal cord. Peripheral neuropathy may coexist or be independently present.
- Concomitant onset of hand and foot paresthesia, disproportionate and severe dorsal column dysfunction, brisk knee jerks with reduced ankle reflexes, and Lhermitte signs indicate a myelopathy accompanying the neuropathy of vitamin B_{12} deficiency.
- Although serum vitamin B_{12} measurement is a widely used screening test, it has technical and interpretive problems and lacks sensitivity and specificity for diagnosing vitamin B_{12} deficiency.
- Holotranscobalamin (transcobalamin-bound cobalamin) represents the metabolically active vitamin B_{12}, and its measurement can be particularly useful in equivocal cases; however, the test has limited worldwide availability.
- The presence of elevated methylmalonic acid and homocysteine levels are important indications for metabolically significant vitamin B_{12} deficiency; the former is more specific than the latter because homocysteine can also be elevated in folate deficiency.
- It is rare to see folate deficiency in isolation. It is particularly important to screen for the deficiency of other nutrients when folate deficiency is detected.
- Red blood cell folate is a more reliable indicator of folate status than plasma folate because it is less affected by short-term fluctuations in folate intake.
- Health care practitioners should exclude coexisting vitamin B_{12} deficiency before instituting folate therapy in patients with folate deficiency.
- Thiamine deficiency should be considered as a possible etiology for neurologic manifestations in any critically ill patient.
- Thiamine has a short half-life, and the body can store only limited amounts; therefore, a continuous dietary supply of thiamine is necessary. A thiamine-deficient diet can result in a clinically significant depletion of the body's stores in just 2 to 3 weeks.
- The most characteristic neurologic disorders resulting from thiamine deficiency are Wernicke encephalopathy, Korsakoff syndrome or Korsakoff psychosis, and beriberi.

- The gait and trunk ataxia seen in Wernicke encephalopathy is caused by cerebellar and vestibular dysfunction, but it may be complicated by a coexisting peripheral neuropathy.
- Peripheral neuropathy typically results from prolonged and mild to moderate thiamine deficiency. A rapid progression that mimics Guillain-Barré syndrome is a well-described neurologic manifestation of thiamine deficiency.
- Serum or plasma thiamine and urinary thiamine levels do not accurately reflect tissue thiamine concentrations. The preferred test is to measure erythrocyte thiamine diphosphate in the whole blood.
- Because parenteral glucose use in patients with a marginal thiamine status can consume the available thiamine and precipitate Wernicke encephalopathy, at-risk patients should be given parenteral thiamine before the administration of glucose or parenteral nutrition.
- Patients with Wernicke encephalopathy, severe malnutrition, or alcohol withdrawal should get higher doses of thiamine. A commonly used regimen in these patients involves giving 500 mg thiamine IV 3 times a day for 2 to 3 days, followed by 250 mg thiamine IV or IM for 3 to 5 days.
- Encephalopathy in people with alcohol use disorder that does not respond to thiamine replacement or to the treatment of suspected withdrawal with benzodiazepines should prompt consideration for niacin deficiency. The peripheral neuropathy seen in niacin deficiency is similar to that seen with thiamine deficiency.
- Symptoms caused by vitamin B_6 deficiency are rare even in the setting of low levels. Peripheral neuropathy may be seen, and vitamin B_6 deficiency can also cause microcytic hypochromic anemia.
- Excess vitamin B_6 consumption, often in doses of 100 mg/d to 200 mg/d for prolonged periods, has been reported to cause a sensory ganglionopathy characterized by sensory ataxia, areflexia, multimodal sensory impairment, and a positive Romberg sign.
- Many years of acquired fat malabsorption are required to deplete vitamin E stores. Only rarely is vitamin E deficiency caused by true dietary insufficiency.
- The prototypic neurologic manifestation of vitamin E deficiency is a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement. Ptosis, pigmentary retinopathy, and ophthalmoparesis may be seen. The phenotype is similar to that of Friedreich ataxia.
- The most common cause of acquired copper deficiency is a prior history of gastric surgery for peptic ulcer disease or bariatric surgery.
- Copper deficiency may be seen with celiac disease even in the absence of gastrointestinal manifestations.
- Excess zinc ingestion is a well-recognized cause of copper deficiency. Zinc decreases copper absorption and is used to manage Wilson disease, a hereditary disorder characterized by copper overload.
- The most common neurologic manifestation of acquired copper deficiency is myelopathy or myeloneuropathy, which resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.
- Thiamine deficiency causes early neurologic problems after bariatric surgery, whereas delayed neurologic problems result from vitamin B_{12} deficiency (in those not on vitamin B_{12} replacement) or copper deficiency.
- Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential small-fiber dysfunction.

ARTICLE 9: PARAPROTEINEMIC NEUROPATHIES

Said R. Beydoun, MD, FAAN; Leila Darki, MD. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1492–1513.

ABSTRACT

OBJECTIVE:

Coexistence of polyneuropathy and gammopathy is a common but potentially challenging situation in clinical practice. This article reviews the clinical, electrophysiologic, and hematologic phenotypes of the paraproteinemic neuropathies and the diagnostic and treatment strategies for each.

LATEST DEVELOPMENTS:

Advances in our understanding of the underlying pathophysiology of various paraproteinemic neuropathies and their corresponding phenotypes have identified potential new therapeutic targets. Therapeutic strategies to diminish anti–myelin-associated glycoprotein (MAG) IgM antibodies have shown partial and inconsistent efficacy; however, antigen-specific immune therapy is being investigated as a novel treatment to remove the presumably pathogenic anti-MAG antibody. Advances in genetic and cell signaling studies have resulted in the approval of Bruton tyrosine kinase inhibitors for Waldenström macroglobulinemia. Monoclonal antibodies are being investigated for the treatment of light chain amyloidosis.

ESSENTIAL POINTS:

Early recognition and treatment of underlying plasma cell disorders improves clinical outcomes in patients with paraproteinemic neuropathy. Despite significant progress, our knowledge regarding underlying mechanisms for paraproteinemic neuropathy is still limited. Clinicians' awareness of clinical phenotypes, electrophysiologic hallmarks, and hematologic findings of the different paraproteinemic neuropathies is crucial to promptly identify and treat patients and to avert misdiagnosis. Multidisciplinary collaboration among specialists, including neurologists and hematologists, is paramount for the optimal treatment of these patients with overlapping conditions.

KEY POINTS

- The risk of progression of monoclonal gammopathy of undetermined significance to myeloma or another related disorder is 1% per year.
- Paraproteinemic neuropathies most commonly occur with IgM paraprotein.
- Serum immunofixation is more sensitive than serum protein electrophoresis and should be performed when a diagnosis of paraproteinemia is considered.
- IgM–myelin-associated glycoprotein (MAG) neuropathy typically manifests with slowly progressive sensory ataxia.
- Anti-MAG antibodies are present in 50% to 65% of patients with IgM neuropathy.
- Prolongation of distal latencies and a short terminal latency index are electrophysiologic hallmarks of IgM anti-MAG neuropathy.
- Patients with IgM MAG neuropathy who have progressive symptoms, including gait ataxia resulting in falls, or those who present with subacute proximal and distal weakness should be treated early before developing permanent deficits due to axonal degeneration.

- Electrodiagnostic features in Waldenström macroglobulinemia can be identical to IgM MAG neuropathy, but axonal or mixed axonal and demyelinating features are more common.
- Although nerve biopsy continues to be the gold standard test for the diagnosis of neurolymphomatosis, neuroimaging and positron emission tomography (PET) increase diagnostic yield.
- CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies) and CANDA (chronic ataxic neuropathy with anti-disialosyl IgM antibodies) are rare sensory ataxic neuropathies associated with disialosyl antibodies, monoclonal proteins, and cold agglutinins characterized by chronic neuropathy with sensory ataxia, areflexia, and motor weakness occasionally involving the ocular motor and bulbar muscles.
- In patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and an IgG or IgA monoclonal gammopathy, the paraprotein is considered to be coincidental and not causative.
- The monoclonal gammopathy in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome is almost always the lambda type.
- A plasma vascular endothelial growth factor (VEGF) level greater than 200 pg/mL is highly specific for the diagnosis of POEMS syndrome in the appropriate clinical setting.
- Screening for concurrent endocrinopathy in patients with POEMS syndrome is indicated and includes testing serum testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, thyroid-stimulating hormone (TSH), free thyroxine, fasting glucose, cortisol, and adrenocorticotropic hormone (ACTH).
- POEMS syndrome should be considered in all cases of refractory CIDP.
- Patients with POEMS syndrome who have one to three bone lesions and no clonal plasma cells detected by bone marrow biopsy may undergo radiation therapy. Patients who have more than three bone lesions or marrow involvement by clonal plasma cells should receive systemic therapy.
- Light chain (AL) amyloidosis neuropathy typically manifests initially as a rapidly progressive painful sensory neuropathy with autonomic dysfunction.
- In AL amyloidosis, the lambda light chain is the most common culprit.
- Amyloid subtyping should be performed when observed pathologically, preferably with mass spectrometry, to exclude hereditary amyloidosis (eg, caused by transthyretin deposition in patients with *TTR* gene variations).

ARTICLE 10: HEREDITARY NEUROPATHIES

Leslie H. Hayes, MD; Reza Sadjadi, MD. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1514–1537.

ABSTRACT

OBJECTIVE:

This article provides an overview of hereditary neuropathies, describes the different hereditary neuropathy subtypes and the clinical approach to differentiating between them, and summarizes their clinical management.

LATEST DEVELOPMENTS:

Increasingly available clinical genetic testing has broadened the clinical spectrum of hereditary neuropathy subtypes and demonstrated a significant overlap of phenotypes associated with a single gene. New subtypes such as *SORD*-related neuropathy and CANVAS (cerebellar ataxia, neuropathy, vestibular areflexia syndrome) have emerged. The optimization of clinical

management has improved gait and motor function in the adult and pediatric populations. Novel therapeutic approaches are entering clinical trials.

ESSENTIAL POINTS:

Hereditary neuropathies constitute a spectrum of peripheral nerve disorders with variable degrees of motor and sensory symptoms, patterns of involvement, and clinical courses.

KEY POINTS

- Charcot-Marie-Tooth (CMT) is the most common hereditary neuropathy and is usually characterized by distal motor loss greater than sensory loss, areflexia, and foot deformity.
- In general, autosomal recessive CMT manifests early, from birth through childhood.
- Patients with CMT1 typically develop weakness in childhood through early adulthood, whereas patients with CMT2 may have early-adult–onset or late-adult–onset symptoms.
- Less common subtypes of hereditary neuropathies include distal hereditary motor neuropathy, a motor-predominant neuropathy, and hereditary sensory and autonomic neuropathy, a sensory-predominant neuropathy.
- Electrodiagnostic testing can help confirm the presence of a neuropathy and distinguish between different subtypes of hereditary neuropathy.
- Negative genetic testing does not exclude a hereditary neuropathy.
- Genetic testing for hereditary neuropathy requires a stepwise approach that may include single-gene targeted testing, a gene panel, or whole-exome or whole-genome sequencing.
- In the pediatric population, it may be appropriate to pursue genetic testing prior to electrodiagnostic evaluation.
- One-third of patients with CMT present in infancy or childhood.
- History of clumsiness or frequent falling can be an early sign of a hereditary neuropathy in the pediatric population.
- Autosomal dominant CMT1A is the most common CMT and has a prototypical phenotype characterized by childhood- to early-adult–onset distal motor weakness, sensory loss, areflexia, and foot deformity.
- Some patients have a demyelinating CMT that can clinically and electrophysiologically mimic chronic inflammatory demyelinating polyradiculoneuropathy.
- Sorbitol dehydrogenase deficiency (SORD-CMT) is a recently discovered autosomal recessive axonal neuropathy with distinctive early plantar flexion weakness.
- CMTX1 is the second-most common CMT subtype, and it may present with episodes of transient neurologic symptoms with white matter abnormalities.
- Hereditary neuropathy with liability to pressure palsies typically results from a deletion in *PMP22*, whereas CMT1A typically results from a duplication in *PMP22*.
- Clinicians should consider hereditary neuropathy with liability to pressure palsies in patients with multiple mononeuropathies, especially when painless.
- Distal hereditary motor neuropathies may share common pathophysiologic mechanisms with other motor neuron diseases, such as hereditary spastic paraplegias.
- Hereditary sensory and autonomic neuropathies can manifest with reduced sensation, pain, or both.
- Peripheral neuropathy can be a component of a broader syndrome involving the central nervous system, other body systems, or both. Examples include Friedreich ataxia, giant axonal neuropathy, and mitochondrial and metabolic disorders.
- Novel therapies for hereditary neuropathies as a whole and for different gene subtypes specifically are an active area of clinical trial interest.

ARTICLE 11: AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

Aaron Izenberg, MD. Continuum (Minneap Minn). October 2023;
29 (5 Sleep Neurology):1538–1563.

ABSTRACT

OBJECTIVE:

This article reviews the clinical spectrum of amyotrophic lateral sclerosis (ALS), its variant presentations, and the approach to diagnosis and management. This review includes a detailed discussion of current and emerging disease-modifying therapies and the management of respiratory and bulbar manifestations of disease. An updated review of ALS genetics and pathophysiology is also provided. This article also touches on several other important motor neuron diseases.

LATEST DEVELOPMENTS:

A new set of simplified diagnostic criteria may help identify patients at earlier stages of the disease. A coformulation of sodium phenylbutyrate and tauroursodeoxycholic acid has been shown to have a significant benefit on disease progression and survival, leading to approval by regulatory authorities in the United States and Canada. An oral formulation of edaravone and an antisense oligonucleotide to a *SOD1* gene variation (tofersen) have also recently been approved by the US Food and Drug Administration (FDA). Phase 3 trials of intrathecal mesenchymal stem cells failed to meet primary end points for efficacy. Updated American Academy of Neurology quality measures for the care of patients with ALS were published in 2023.

ESSENTIAL POINTS:

There has been continued progress in ALS genetics, diagnosis, and disease-modifying therapies. However, we still lack a definitive biomarker or a treatment that can halt the progression or reverse the course of disease. The evolving understanding of the genetic and pathophysiologic underpinnings of disease offers promise for more effective and clinically meaningful treatments in the future.

KEY POINTS

- Amyotrophic lateral sclerosis (ALS) has a heterogeneous clinical phenotype. The three most common presentations are that of lower limb, upper limb, and bulbar weakness, with each accounting for 25% to 30% of patients.
- Distal limb muscles are typically affected first in patients with ALS, with subsequent progression to proximal muscles. Upper motor neuron involvement results in more stiffness and slowness of movement and usually causes less weakness than lower motor neuron loss.
- Up to 30% of patients with ALS may develop pseudobulbar affect.
- Orthopnea and symptoms of sleep-disordered breathing are characteristic features of respiratory involvement in ALS.
- An isolated upper motor neuron presentation often evolves into a conventional ALS phenotype.
- Recent consensus diagnostic criteria suggest a classification of probable primary lateral sclerosis for patients with isolated upper motor neuron involvement between 2 and 4 years from symptom onset and definite primary lateral sclerosis beyond 4 years.
- Progressive muscular atrophy and primary lateral sclerosis both have a more favorable prognosis than ALS.

- There is no gold-standard diagnostic test or biomarker for ALS. Although all patients should undergo electrophysiologic testing, imaging and bloodwork should be guided by the clinical phenotype.
- The Gold Coast diagnostic criteria for ALS are simpler than the revised El Escorial and Awaji criteria and may be of benefit for diagnosing patients earlier in the disease.
- Familial ALS occurs in at least 10% of patients. However, pathogenic gene variations may be found in up to 15% of patients diagnosed with sporadic ALS.
- Variations in the *C9orf72* and *SOD1* genes remain the most common genetic causes of familial ALS. However, the list of recognized variations is growing.
- Genetic testing should be offered to all patients with a family history of ALS and to those with comorbid frontotemporal dementia. There will likely also be a role for more routine testing in all patients with ALS given the frequency of pathogenic variations in sporadic disease and the ongoing development of gene-based therapies.
- Disease-modifying therapies for sporadic ALS include riluzole, edaravone, and the coformulation of sodium phenylbutyrate and tauroursodeoxycholic acid. All these agents result in modestly slowed progression, prolonged survival, or both.
- Noninvasive ventilation improves quality of life and survival in ALS and should be initiated at a forced vital capacity of 50% or possibly earlier.
- Insertion of a gastrostomy tube should be considered in patients with significant weight loss or dysphagia. Placement should ideally take place before the forced vital capacity is 50%.
- Despite the development of staging and prognostic models, accurate prediction of ALS progression remains challenging.
- Kennedy disease is an X-linked motor neuron disease with associated endocrine features (such as gynecomastia), increased serum creatine kinase, and concurrent sensory neuronopathy.
- Monomelic amyotrophy is a lower motor neuron disease with asymmetric upper limb involvement that progresses for 1 to 5 years and typically affects males in late adolescence. The workup should include a cervical spine MRI with flexion sequences.

ARTICLE 12: SPINAL MUSCULAR ATROPHY

Maryam Oskoui, MD, FAAN; Laurent Servais, MD, PhD. Continuum (Minneap Minn). October 2023; 29 (5 Sleep Neurology):1564–1584.

ABSTRACT

OBJECTIVE:

This article provides a comprehensive overview of the diagnostic assessment and treatment of individuals with spinal muscular atrophy (SMA) due to homozygous deletions of *SMN1*.

LATEST DEVELOPMENTS:

In recent years, most states have incorporated SMA in their newborn screening panel. To provide the earliest diagnosis possible after symptom onset, vigilance is needed for births in states without newborn screening for SMA and when compound heterozygotes are missed by newborn screening programs. Supportive care for respiratory, nutritional, and orthopedic health impacts outcomes and is the cornerstone of care. Adaptive equipment, including assistive home technology, enables affected individuals to gain autonomy in their daily activities. Pharmacologic treatments approved by the US Food and Drug Administration (FDA) include three drugs that increase deficient survival motor neuron protein levels through *SMN1*- or *SMN2*- directed

pathways: nusinersen, onasemnogene abeparvovec, and risdiplam. Efficacy for these trials was measured in event-free survival (survival without the need for permanent ventilation) and gains in functional motor outcomes. Earlier treatment is most effective across all treatments.

ESSENTIAL POINTS:

The diagnostic and therapeutic landscapes for SMA have seen dramatic advancements in recent years, improving prognosis. Optimized supportive care remains essential, and vigilance is needed to define the new natural history of this disease.

KEY POINTS

- The birth incidence of spinal muscular atrophy has a wide variability although it remains a rare disorder, with approximately 1 in 10,000 births affected.
- The carrier frequency for spinal muscular atrophy is estimated to be as high as 1 in 50 individuals in some populations.
- 5q spinal muscular atrophy is diagnosed by genetic testing which usually demonstrates homozygous deletion of exon 7, exon 8, or both, in the *SMN1* gene. In 5% of symptomatic individuals, a compound heterozygous state is present.
- Survival motor neuron protein is expressed in all cells with highest expression in late fetal and early postnatal development; however, motor neurons are most susceptible to low levels of expression.
- Levels of phosphorylated neurofilaments, a well-established biomarker of neuronal destruction, are dramatically increased at birth in babies with two copies of *SMN2*, even before symptom onset.
- Early recognition of patients with spinal muscular atrophy with preserved or even brisk muscle stretch reflexes at presentation can reduce diagnostic delay and allow earlier treatment initiation.
- Neurophysiologic testing is no longer required in the diagnostic assessment of spinal muscular atrophy to establish a diagnosis; however, compound motor action potential amplitudes can be an indirect measure of disease progression and useful to monitor in patients with four copies of survival motor neuron type 2 in settings where treatment cannot be initiated presymptomatically.
- Shortly after the identification of the first presymptomatic cases through screening programs, a broad consensus was reached that patients with spinal muscular atrophy with two or three copies of *SMN2* should be treated immediately.
- Recommended best practices with developmental surveillance and respiratory and nutritional support are the cornerstone of treatment in spinal muscular atrophy.
- Measuring spinal muscular atrophy treatment response in clinic should be based on appropriate motor function measures by phenotypes and age, as well as individual goals of care to guide shared decision making.
- Nusinersen 12 mg administered by intrathecal injection has been approved by the US Food and Drug Administration since 2016 and has demonstrated efficacy across a wide range of spinal muscular atrophy phenotypes.
- IV onasemnogene abeparvovec shows the highest efficacy if initiated presymptomatically in patients with two or three copies of *SMN2* and has been approved by the US Food and Drug Administration since May 2019 for treatment of children younger than 2 years old.
- Risdiplam is an orally administered, systemically distributed molecule approved by US Food and Drug Administration in August 2020 and has demonstrated efficacy across a broad range of phenotypes in patients younger than 25 years old.
- There is currently no evidence of efficacy for combining spinal muscular atrophy therapies aimed at increasing survival motor neuron protein production. The additional cost, the burden for patients, and additional risk of adverse effects should be considered in parallel with the absence of evidence of additional benefit from combined therapies.
- A shared informed decision process is encouraged when choosing which spinal muscular atrophy disease-modifying therapy to initiate while considering available evidence, patient preferences, and availability of treatments.

Issue Overview

Peripheral Nerve and Other Motor Neuron Disorders, Volume 29, Number 5, October 2023

Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Peripheral Nerve and Motor Neuron Disorders issue, participants will be able to:

- Initiate diagnostic evaluation in patients with suspected peripheral nerve disease by applying a framework for clinical diagnosis
- Discuss the clinical features, diagnostic criteria, differential diagnosis, pathogenesis, prognosis, and insights into the current and future diagnostic and therapeutic interventions of Guillain-Barré syndrome
- Identify the types of chronic demyelinating neuropathies and differentiate and treat immune-mediated demyelinating neuropathies
- Identify the common causes of autoimmune axonal neuropathy and develop appropriate clinical evaluation and management strategies based on subtype
- Diagnose and manage the spectrum of peripheral neuropathies associated with diabetes
- Discuss the infectious causes of peripheral neuropathies and the types of neuropathies associated with them
- Perform the clinical diagnosis, workup, and management of the most clinically relevant toxic neuropathies
- Discuss the clinical presentation, evaluation, and management of peripheral neuropathies caused by nutritional deficiencies
- Identify common clinical phenotypic, electrophysiologic, and hematologic features of each paraproteinemic neuropathy and tailor the appropriate diagnostic investigation and multidisciplinary treatment approach
- Guide the clinical evaluation of patients with suspected hereditary neuropathy and discuss the major clinical phenotypes and common genotypes of hereditary neuropathies
- Describe the clinical spectrum, diagnostic process, evolving genetic landscape, and approach to management for amyotrophic lateral sclerosis
- Discuss the diagnostic assessment of individuals with spinal muscular atrophy, available treatment options, and key outcome measures
- Identify the role of multidisciplinary care in the management of patients with neuromuscular disorders

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Peripheral Nerve and Motor Neuron Disorders issue covers the following core competencies:

- Patient Care and Procedural Skills
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

Contributors

Kelly Gwathmey, MD, ***Guest Editor***
Associate Professor of Neurology; Neuromuscular Medicine Division Chair, Virginia Commonwealth University, Richmond, Virginia

Relationship Disclosure: Dr Gwathmey has received personal compensation in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Alexion Pharmaceuticals, Inc, and in the range of $500 to $4999 for serving as a consultant for Alexion Pharmaceuticals, Inc, argenx, UCB S.A., and Xeris Biopharma and for serving on a speakers bureau for Alexion Pharmaceuticals, Inc.

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Said R. Beydoun MD, FAAN
Professor of Clinical Neurology; Richard Angus Grant Sr. Chair in Neurology; Division Chief, Neuromuscular Medicine; Program Director, Clinical Neurophysiology, Keck School of Medicine of USC, Los Angeles, California

Relationship Disclosure: Dr Beydoun has received personal compensation in the range of $500 to $4999 for serving as a consultant for Amylyx Pharmaceuticals, Biogen, Mitsubishi Chemical Group Corporation, Octapharma USA, Inc, and UCB S.A. and on a speakers bureau for Grifols S.A.; in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, Alnylam Pharmaceuticals, Inc, argenx, Janssen Global Services, LLC, and Takeda Pharmaceutical Company Ltd and on speakers bureaus for Amylyx Pharmaceuticals and CSL; and in the range of $10,000 to $49,999 for serving as a consultant for CSL and on speakers bureaus for Alexion Pharmaceuticals, Inc, Alnylam Pharmaceuticals, Inc, argenx, and Takeda Pharmaceutical Company Ltd. The institution of Dr Beydoun has received research support from Alexion Pharmaceuticals, Inc, Amylyx Pharmaceuticals, argenx, Genentech, Inc, Janssen Global Services, LLC, Regeneron Pharmaceuticals Inc, Sanofi, the Sean M. Healey & AMG Center for ALS, UCB S.A.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Beydoun discusses the unlabeled/investigational use of ibrutinib, IV immunoglobulin, and rituximab for the treatment of IgM-myelin-associated glycoprotein polyneuropathy.

Aimee Boegle, MD, PhD
Instructor, Harvard Medical School; Director, Neuromuscular Medicine Fellowship Associate Program Director, Neurology Residency, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Relationship Disclosure: Dr Boegle has received publishing royalties from Wolters Kluwer Health N.V.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Boegle discusses the unlabeled use of doxycycline, amoxicillin, and cefotaxime for the treatment of Lyme disease and the unlabeled use of gabapentin, lamotrigine, oxcarbazepine, pregabalin, selective norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine), topical anesthetics (eg, capsaicin, lidocaine), and tricyclic antidepressants (eg, amitriptyline, nortriptyline) for the treatment of neuropathic pain.

Brian Callaghan, MD, FAAN

Associate Professor of Neurology, Department of Neurology, University of Michigan, Ann Arbor, Michigan

Relationship Disclosure: Dr Callaghan has received personal compensation in the range of $500 to $4999 for serving as an editorial board member for the American Academy of Neurology, a consultant for Dynamed (EBSCO Industries, Inc), and a grant reviewer for the National Institutes of Health; in the range of $10,000 to $49,999 for serving as an expert witness for medicolegal work; and in the range of $50,000 to $99,999 for serving as an expert witness for the Vaccine Injury Compensation Program. The institution of Dr Callaghan has received research support from the American Academy of Neurology, JDRF (5COE-2019-861-S-B), the National Institute of Diabetes and Digestive Kidney Diseases (R01DK115687), and Veterans Affairs Clinical Science and Research Development.

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Leila Darki, MD

Assistant Professor of Clinical Neurology, Keck Medicine of USC, Los Angeles, California

Relationship Disclosure: Dr Darki has received personal compensation in the range of $0 to $499 for serving as a consultant for Guidepoint Global LLC and in the range of $500 to $4999 for serving as a consultant for Trinity Partners, LLC, and on scientific advisory or data safety monitoring boards for Amylyx Pharmaceuticals and Global Access Meetings.

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Melissa Elafros, MD, PhD

Assistant Professor, Department of Neurology, University of Michigan, Ann Arbor, Michigan

Relationship Disclosure: The institution of Dr Elafros has received research support from the National Center for Advancing Translational Sciences (UL1TR002240), the National Institute of Diabetes and Digestive and Kidney Diseases (P30-DK-02926 and P30-DK089503), and the National Institute of Neurologic Disorders and Stroke (5R25NS089450).

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Karissa Gable, MD

Associate Professor, Department of Neurology, Neuromuscular Division, Duke University Medical Center, Durham, North Carolina

Relationship Disclosure: Dr Gable has received personal compensation in the range of $500 to $4999 for serving as a consultant for Cowen Inc, MJH Life Sciences, WebMD, LLC, and on the scientific advisory or data safety monitoring boards for argenx, Immunovant, Inc, and Ultragenyx Pharmaceutical Inc and has received personal compensation in the range of $5000 to $9999 for serving on scientific advisory or data safety monitoring boards for Sanofi and Takeda Pharmaceutical Company Ltd and as a lecturer for WebMD, LLC.

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Ali Habib, MD

Associate Professor; Director, Electrodiagnostic Laboratory, Department of Neurology, University of California, Irvine, California

Relationship Disclosure: Dr Habib has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for the National Institutes of Health/National Institute of Neurological Disorders and Stroke and UCB S.A., and as a consultant for Pfizer Inc and in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, argenx, Genentech, Inc, Immunovant, Inc, and UCB S.A., and for serving on speakers bureaus for Alexion Pharmaceuticals, Inc, and argenx. The institution of Dr Habib has received research support from Alexion Pharmaceuticals, Inc, argenx, Cabaletta Bio, Inc, Genentech, Inc, Immunovant, Inc, Regeneron Pharmaceuticals Inc, and UCB S.A.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Habib discusses the unlabeled/investigational use of IV immunoglobulin for the treatment of Guillain-Barré syndrome.

Leslie H. Hayes, MD

Instructor in Neurology, Harvard Medical School; Attending Physician, Boston Children's Hospital, Boston, Massachusetts

Relationship Disclosure: Dr Hayes has received personal compensation in the range of $500 to $4999 for serving as a consultant for PTC Therapeutics.

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Terry D. Heiman-Patterson, MD

Professor of Neurology; Director MDA/ALS Center of Hope, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania

Relationship Disclosure: Dr Heiman-Patterson has received personal compensation in the range of $500 to $4999 for serving as a consultant for ITF Pharma, Mitsubishi Tanabe Pharma America, and Samus Therapeutics, Inc, and on scientific advisory or data safety monitoring boards for Amylyx Pharmaceuticals, Biogen, Biohaven Ltd, Cytokinetics, and Mitsubishi Tanabe Pharma America.

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Aaron E. Izenberg, MD

Assistant Professor Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Relationship Disclosure: Dr Izenberg has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Biogen, F. Hoffman-La Roche Ltd, and Sanofi.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Izenberg reports no disclosure.

Peter Jin, MD

Assistant Professor, Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland

Relationship Disclosure: Dr Jin has received personal compensation in the range of $0 to $4999 for serving as a consultant for Ionis Pharmaceuticals.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Jin reports no disclosure.

Noah Kolb, MD
Associate Professor of Neurological Sciences, University of Vermont, Burlington, Vermont

Relationship Disclosure: Dr Kolb has received personal compensation in the range of $0 to $499 for serving as a consultant for Eisana Corp; in the range of $500 to $4999 for serving as a consultant for Abalone Bio, Inc, Alexion Pharmaceuticals, Inc, Lilly, and UCB S.A.; in the range of $5000 to $9999 for serving as a consultant for the National Institute of Neurological Disorders and Stroke and for serving as an expert witness for Locks Law and for Ralston, Pope & Diehl; and in the range of $10,000 to $49,999 for serving as an expert witness for Walkup, Melodia, Kelly & Schoenberger. The institution of Dr Kolb has received research support from the National Cancer Institute.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Kolb discusses the unlabeled use of baclofen-amitriptylineketamine, gabapentin, lidocaine, mexiletine, nortriptyline or amitriptyline, and pregabalin for the treatment of neuropathic pain.

Neeraj Kumar, MD
Professor of Neurology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota

Relationship Disclosure: Dr Kumar reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Kumar reports no disclosure.

Brendan McNeish, MD
Assistant Professor, Department of Physical Medicine Rehabilitation and Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania
Relationship Disclosure: Dr McNeish has received research support in the range of $100,000-$499,999 from the National Institutes of Health (NIA P30AG02482).

Unlabeled Use of Products/Investigational Use Disclosure: Dr McNeish discusses the unlabeled use of baclofen-amitriptylineketamine, gabapentin, lidocaine, mexiletine, nortriptyline or amitriptyline, and pregabalin for the treatment of neuropathic pain.

Pushpa Narayanaswami, MD, FAAN
Associate Professor of Neurology, Harvard Medical School; Vice Chair, Clinical Operations, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Relationship Disclosure: Dr Narayanaswami has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Alexion Pharmaceuticals, Inc, argenx, and Sanofi and for serving as a consultant for Novartis Pharmaceuticals Corporation; in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Janssen Global Services, LLC, and for serving as an editor, associate editor, or editorial advisory board member for *Muscle & Nerve*; and in the range of $10,000 to $49,999 for serving as a consultant for UCB S.A. Dr Narayanaswami has stock in Doximity, Inc, Dr Reddy's Laboratories Ltd, Moderna, Inc, Pfizer Inc, and Viatris Inc. Dr Narayanaswami has noncompensated relationships as a member of the boards of directors with the American Association of Neuromuscular & Electrodiagnostic Medicine and the Myasthenia Gravis Foundation Of America, Inc, that are relevant to the American Academy of Neurology interests or activities. The institution of Dr Narayanaswami has received research support from Alexion Pharmaceuticals, Inc

Unlabeled Use of Products/Investigational Use Disclosure: Dr Narayanaswami discusses the unlabeled use of doxycycline, amoxicillin, and cefotaxime for the treatment of Lyme disease and the unlabeled use of gabapentin, lamotrigine, oxcarbazepine, pregabalin, selective norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine), topical anesthetics (eg,

capsaicin, lidocaine), and tricyclic antidepressants (eg, amitriptyline, nortriptyline) for the treatment of neuropathic pain.

Maryam Oskoui, MD, FAAN
Associate Professor, Department of Pediatrics, Department of Neurology and Neurosurgery, McGill University; Director, Division of Pediatric Neurology, McGill University Health Center, Montreal, Quebec, Canada

Relationship Disclosure: Dr Oskoui has a noncompensated relationship as a member of the medical and scientific advisory committee with Muscular Dystrophy Canada that is relevant to the American Academy of Neurology (AAN) interests or activities and has received personal compensation in the range of $500 to $4999 for serving as a member of the board of directors for the Association des Neurologues du Québec. The institution of Dr Oskoui has received research support from Biogen, the Canadian Institutes of Health Research, Genetech, Inc, Muscular Dystrophy Canada, and Santhera Pharmaceuticals.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Oskoui discusses the unlabeled/investigational use of celecoxib, E1v1.11, flunarizine, moxifloxacin, reldesemtiv rigosertib, salbutamol, and securinine for the treatment of spinal muscular atrophy.

Reza Sadjadi, MD
Assistant Professor in Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Relationship Disclosure: Dr Sadjadi has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Alnylam Pharmaceuticals, Inc, and the Dysimmune Diseases Foundation. The institution of Dr Sadjadi has received research support from the American Academy of Neurology.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Sadjadi reports no disclosures.

Laurent Servais, MD, PhD
Professor of Paediatric Neuromuscular Diseases, University of Oxford, Oxford, United Kingdom

Relationship Disclosure: Dr Servais has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for Lupin Pharmaceuticals, Inc, and FibroGen, Inc, and as a consultant for Affinia Healthcare, Anagenesis Biotechnologies, Audentes Therapeutics, Catabasis Pharmaceuticals, Evox Therapeutics, Flamingo Therapeutics, RegenexBio Inc, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc; in the range of $5000 to $9999 for serving as a consultant for Biogen and Novartis AG; and in the range of $10,000 to $49,999 for serving as a consultant for F. Hoffman-La Roche Ltd and Pfizer Inc.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Servais discusses the unlabeled/investigational use of celecoxib, E1v1.11, lunarizine, moxifloxacin, reldesemtiv rigosertib, salbutamol, and securinine for the treatment of spinal muscular atrophy.

Jennifer Tracy, MD
Assistant Professor of Neurology, Division of Neuromuscular Medicine, Department of Neurology, Mayo Clinic, Rochester, Minnesota

Relationship Disclosure: Dr Tracy reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Tracy reports no disclosure.

Dr Tracy died September 26, 2023.

Waqar Waheed, MD

Professor of Neurology, Vice-Chair Department of Neurological Sciences, The University of Vermont and The University of Vermont Medical Center, Burlington, Vermont
Relationship Disclosure: Dr Waheed has received personal compensation in the range of $500 to $4999 for serving on a scientific advisory or data safety monitoring board for UCB S.A.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Waheed discusses the unlabeled/investigational use of IV immunoglobulin for the treatment of Guillain-Barré syndrome.

Self-Assessment and CME Test Writers

Douglas J. Gelb, MD, PhD, FAAN
Professor of Neurology, University of Michigan, Ann Arbor, Michigan

Relationship Disclosure: Dr Gelb has received personal compensation in the range of $500 to $4900 for serving as a multiple-choice question writer for *Continuum* with the American Academy of Neurology. Dr Gelb has received publishing royalties from a publication relating to health care.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Gelb reports no disclosure.

Nuri Jacoby, MD, FAAN
Associate Professor of Clinical Neurology, SUNY Downstate Health Sciences University; Attending Neurologist, Maimonides Medical Center, Brooklyn, New York

Relationship Disclosure: Dr Jacoby has received personal compensation in the range of $500 to $4999 for serving as a multiple-choice question writer for *Continuum* with the American Academy of Neurology and on scientific advisory or data safety monitoring boards for Alexion Pharmaceuticals, Inc and argenx and in the range of $5000 to $9999 for serving as an expert witness. The institution of Dr Jacoby has received research support from the American Board of Psychiatry and Neurology.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Jacoby reports no disclosure.

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